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Chapter 1

Introduction and outline of the thesis

Introduction

Breast cancer screening program

Worldwide breast cancer (BC) is the most common cancer and the leading cause of cancer death in women both in the developed and developing world.[1] In 2008 1.38 million women were diagnosed with BC, which is 23 per cent of all cancers, and 458.000 die from this disease annually.[1] In the Netherlands one in eight women will get BC during her life.[2,3]

BC screening with mammography has been introduced to detect BC before it is clinically apparent, thereby obtaining earlier detection with the potential to reduce BC mortality.[4] The first mammography screening trial was performed in New York in the 1960s. Subsequently several trials were performed in the 1970s and 1980s in Sweden, the United Kingdom, and Canada.[4,5] In the Netherlands, the first experimental BC screening was introduced in 1974. A nationwide screening program was initiated in 1988, with full coverage in 1997.[5,6] Women in the age between 50 and 75 years receive an invitation for a BC screening mammogram every two years, which comes down to approximately one million women annually.[5] The attendance rate of the BC screening program is around 80 per cent, with a recall rate up to 2 per cent and a false-positive rate of 66 per cent after recall.[5,6,7] In comparison, in the United States the recall rate is 11 per cent after a first screening mammogram and 7 per cent after a subsequent screening mammogram and in the United Kingdom these percentages are 7 per cent and 4 per cent respectively.[8]

In the Western World the BC incidence is still increasing, but over decades the BC mortality has considerably decreased.[1] One is inclined to think that this reduction of BC mortality is the result of earlier detection by the BC screening program. However, recent studies suggested that this decline in BC mortality is accomplished by the improvements of adjuvant BC treatment[9,10,11], and that screening has little detectable impact on BC mortality.[12,13] A recent Cochrane review revealed limited evidence for the idea that BC screening reduces BC mortality. The decrease in BC mortality of 15 per cent corresponds with an absolute risk reduction of 0.05 per cent.[4] In addition, the number of mastectomy is 20 per cent higher in women who are attending the BC screening program.[4] Whether the enhanced BC survival has been achieved by earlier detection through screening, better BC awareness, or by improved treatments is important to consider, because of the substantial disadvantages of the BC screening program, such as overdiagnosis, overtreatment, and a false-positive screening mammogram.[4,14] Screening causes 30 per cent overdiagnosis and overtreatment,

and therefore, the harms of unnecessary treatment could outdo any potential benefit of the BC screening.[4] The risk for a false-positive screening mammogram is estimated to be 49 per cent after ten mammograms in the United States and up to 21 per cent in Norway.[15,16] Women with a false-positive screening mammogram report ongoing anxiety with impaired quality of life (QoL) during and after the diagnostic work-up.[4,17-20]
Thus, the disadvantages of the BC screening program are substantial and moreover, recent data has suggested that screening has little detectable impact on BC mortality.[4,12,13] Therefore, we questioned whether the advantages still justify the disadvantages of the BC screening program. To contribute to this ongoing discussion, we believe it is important to determine the impact of an abnormal screening mammogram (ASM) on women's psychological distress (state anxiety, depressive symptoms) and QoL.

Breast cancer and distress and quality of life

Up to 50 per cent of women diagnosed with BC experience higher levels of anxiety and distress during the diagnostic process.[21-24] In women with BC, the prevalence of depression and depressive symptoms vary from 1.5 to 46 per cent.[25] Before being diagnosed with BC, 28 per cent of women experience high anxiety in combination with depressive symptoms.[26] This fact was found to be a major predictor for QoL 12 and 24 months after BC surgery.[26] Women with benign breast disease (BBD) go through similar emotions.[21-24] Previous studies have revealed a negative impact of the personality characteristic trait anxiety, which describes anxiety proneness[27], on momentary anxiety, depressive symptoms, and QoL in both women with BC and BBD.[22,24,28-30] Moreover, trait anxiety determined the impaired QoL in women with breast disease, regardless of the diagnosis being BC or BBD.[31]

Aim and design of the study

Thus, women report increased levels of anxiety, distress, depressive symptoms and impairment in QoL when undergoing the diagnostic work-up for BC (after an ASM), irrespective of being diagnosed with BC or BBD. We believe that a tailor-made follow-up protocol would be useful to prevent the adverse psychological consequences in women (with high trait anxiety) during and after the diagnostic process for (malignant) breast disease. Before implementing such a protocol, we need to establish a number of things. Firstly, more insight should be gained about the extent of the psychological consequences of BC screening for women eventually diagnosed with BBD. Secondly, the adverse psychological effects could

be a reason for an increase in health care utilization during and after the diagnostic process for BC and BBD, especially in women with high trait anxiety. However, limited research concerning health care utilization in women with BC or BBD is performed. It is important to determine the patterns and predictors of health care utilization in women with breast disease, since it will be possible with this knowledge to anticipate to their needs and eventually adjust the current follow-up protocol guidelines. Thirdly, it is important to know whether the chronically anxious women are *always* more anxious, experience more depressive symptoms, and have an impaired QoL when confronted with a medical problem or whether this depends on the severity of diagnosis they are facing.

Women who were referred to the outpatient breast clinic with a palpable lump in the breast or an ASM, were asked to participate in this study. The aim of the first part of this thesis was to examine the impact of being recalled for further diagnostic procedures after an ASM on women's psychological distress (state anxiety, depressive symptoms) and QoL. Women diagnosed with BC or BBD after an ASM were compared. Furthermore, women were compared with regard to the timing of the screening mammogram (first versus repeat), and women with BBD referred after an ASM or referred with a palpable lump in the breast were compared. These two comparisons have not been performed before. To our knowledge, this is the first study analysing the influence of the personality characteristic trait anxiety on the psychological consequences in women with a false-positive screening mammogram. In addition, in our study the questionnaires were completed before the diagnostic procedures were performed, thus *before* the diagnosis BC or BBD was known. This renders a true baseline measurement.
Thus far, only a few studies have examined the impact of an ASM on QoL. However, the majority of studies analysing "QoL" in women with BC or BBD measured health status, often referred to as health-related QoL. This is not equivalent to QoL and, therefore, not considered interchangeable. Health status measures the impact of disease on functioning whereas QoL also reflects to what extent a patient is bothered by these limitations in daily life.[31] Therefore, in our study we measured QoL with the WHOQOL questionnaire which askes about satisfaction and not merely functioning.

The second part of this thesis focuses on the impact of the personality characteristic trait anxiety on health care utilization, psychological distress (state anxiety, depressive symptoms) and QoL in women with breast disease. Firstly, we analysed health care utilization and its predictors in women with BC or BBD. So far, this is the first study examining the impact of the personality characteristic trait

anxiety on health care utilization. Secondly, we hypothesized that the severity of diagnosis, i.e. being confronted with a possible malignant breast disease, will also be an important predictor for psychological distress, in addition to the personality characteristic trait anxiety. Therefore, we compared women with BC or BBD with women with gallstone disease awaiting a laparoscopic cholecystectomy. To our knowledge, this comparison has not been performed before. The group of women with gallstone disease was chosen because it was previously found that trait anxiety had a negative impact on QoL and persisting symptoms in this group.[32,33]

Questionnaires

The questionnaires assessed personality (STAI-Trait, NEO-FFI), state anxiety (STAI-State), depressive symptoms (CES-D), fatigue (FAS) and QoL (WHOQOL-100 and WHOQOL-Bref). Questionnaires were completed at baseline, and one, three, six and twelve months after the definitive diagnosis or surgery.

The personality trait neuroticism was measured by the neuroticism part (12-items) of the Neuroticism-Extraversion-Openness-Five Factor Inventory (NEO-FFI).[34,35] Neuroticism weighs emotional instability against emotional stability. The reliability and validity of this questionnaire are good.[34]

The State and Trait Anxiety Inventory (STAI) was used to assess state anxiety and the personality characteristic trait anxiety. State anxiety is a momentary emotional condition characterized by subjective feelings of apprehension and tension, and heightened autonomic nervous system activity. Trait anxiety concerns differences in individuals in the disposition to respond to stressful situations, such as a possible diagnosis of BC, with varying amounts of stress.[27,36] The original and short versions of the STAI-Trait and STAI-State were used. The psychometric properties of both versions are well established and considered good.[27,36-39]

Depressive symptoms were measured with the Center for Epidemiological Studies-Depression Scale (CES-D). The CES-D includes six components: depressed mood, feelings of guilt and worthlessness and hopelessness, psychomotor retardation, loss of appetite and sleep disturbance. However, no component scores can be calculated, only a total score may be used. It measures both the presence and the degree of depressive symptoms.[40] The psychometric properties are good.[40,41]

Fatigue was scored using the 10-items Fatigue Assessment Scale (FAS).[42] It is a questionnaire that measures perceived fatigue and exhaustion. The reliability and validity of the FAS appear to be good in women with breast problems[43] and the general population.[42,44]

The World Health Organization Quality of Life assessment instrument (WHOQOL-100) is a generic, cross-culturally multidimensional questionnaire.[45,46] It consists of

100 items assessing 24 facets of QoL within six domains (Physical health, Psychological health, Level of independence, Social relationships, Environment and Spirituality) and a general evaluative facet (Overall QoL and General health). The reliability and validity of this questionnaire are good for women with breast disease.[47] In addition, the WHOQOL-Bref has also been used, which is the short version of the WHOQOL-100 questionnaire.[48] The WHOQOL-Bref consists of questions assessing QoL within four domains (Physical health, Psychological health, Social relationships and Environment) and a general evaluative facet (Overall QoL and general health). The psychometric properties of the WHOQOL-Bref are considered good (WHOQOL) also in women with benign breast disease.[49]

Outline of this thesis

Chapter two describes the effect of an ASM on QoL and state anxiety until one year after diagnosis. Women with a false-positive screening mammogram were compared with women diagnosed with BC after an ASM. In addition, the effect of trait anxiety on QoL and state anxiety was examined.

In **chapter three** the adverse psychological consequences after an ASM in women with BBD were analysed. We were especially interested in the timing of the screening mammogram, i.e. first or repeat screening mammogram, and the effect on psychological distress (anxiety, depressive symptoms) and QoL. The impact of trait anxiety on these psychological factors was also analysed.

In **chapter four** we examined whether the previously found adverse psychological effects are found in all women diagnosed with BBD or in particular in women referred after an ASM. Women with a false-positive screening mammogram were compared with women with a palpable lump in the breast and diagnosed with BBD. The influence of trait anxiety on the psychological distress was studied.

In **chapter five** we evaluated the health care utilization and its predictors in women with BC or BBD during the first year following the diagnosis. Women diagnosed with BC were compared with women with BBD, and the influence of trait anxiety on health care utilization was studied.

In **chapter six** we analysed whether high state anxiety and depressive symptoms previously found in women with BC or BBD were determined solely by the personality characteristic trait anxiety or whether it was caused by personality in combination with the severity of diagnosis, a possible life-threatening disease (i.e. BC). To examine this, we compared women with breast disease before diagnosis is known (BC or BBD) with women with a non life-threatening disease, i.e. gallstone disease awaiting an elective laparoscopic cholecystectomy.

In **chapter seven** we compared women with BC or BBD with women with gallstone disease awaiting a laparoscopic cholecystectomy to determine the impact of trait anxiety and/or the severity of diagnosis on QoL.
Finally, **chapter eight** contains the summary and discussion on the study results, and the clinical implications with the future perspectives.

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Chapter 2

Effect of abnormal screening mammogram on quality of life

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Abstract

Background
Screening for breast cancer reduces breast-cancer related mortality. Advantages of screening are explained clearly, but its disadvantages are underrepresented in consent folders.

Methods
In September 2002 a prospective, longitudinal study started concerning quality of life (QoL) in women with breast disease. Between September 2002 and January 2007, 385 women with an abnormal screening mammogram were included. Of these, 152 women were diagnosed with breast cancer (BC group) and 233 had a false-positive result (FP group). Questionnaires concerning anxiety (State and Trait Anxiety Inventory) and QoL (World Health Organization Quality of Life assessment instrument 100) were completed before diagnosis and one, three, six and twelve months later.

Results
The BC group was significantly older (60 versus 57 years, $p<0.001$); significantly more histological biopsies were needed in the FP group ($p<0.001$). Almost 60 per cent of the FP group revisited the outpatient clinic in the first year. Trait anxiety had a profound influence on QoL. Women in the FP group with a high score on trait anxiety had lowest QoL on all measurement ($p<0.001$). They also reported more feelings of anxiety compared with women in the FP group with a lower trait anxiety score, and women in the BC group with a low trait anxiety score ($p<0.001$).

Conclusions
Women with a false-positive diagnosis of screen-detected breast cancer had a low QoL and feelings of anxiety, especially when they scored high on trait anxiety. This effect lasted for at least one year.

Introduction

Cancer screening is intuitively appealing, and common sense dictates that early detection is good and without risks.[1,2] Most screening programs for breast cancer (BC) have proven successful in decreasing BC related mortality.[3,4] In the Netherlands the invitation to undergo mammography sent to women every two years claims survival advantages, but does not mention the potential uncertainties and pitfalls in a clear way.[5] The Dutch screening program has a 1 per cent recall rate for assessment. It is known that common psychological reactions during detection, diagnosis, and treatment of cancer include anxiety and depression.[6,7] Being recalled for further investigation after an abnormal screening mammogram is a stressful experience for many women.[8] Short-term effects include depressive symptoms and anxiety, especially when an additional biopsy is necessary.[9]
It is not only the woman who decides to participate in BC screening who has the anxiety and psychological burden, her family and social support are included.
In this prospective, longitudinal study the possible risks and negative side-effects of false-positive results in BC screening were examined. The study analysed the effects of (possibly) unnecessary diagnostic procedures and treatment, and the impact of a false-positive result on quality of life (QoL).

Patients and methods

Screening

In the southern part of the Netherlands, BC screening started in 1991, and full coverage was reached in 1996. Since then, the attendance rate has remained about 80 per cent. Women aged 50-75 years receive a standard invitation every two years. The invitation includes a set date and time, and an information leaflet. This leaflet informs women how the screening mammogram is done. Since 2006 information has also been included about the number of women who are referred to the hospital because of abnormalities on the mammogram.

Patients

Women who were referred to the outpatient clinic of the St. Elisabeth Hospital (patient accrual started September 2002), Maasland Hospital (since August 2004) and Jeroen Bosch Hospital (since January 2006), with an abnormality on a screening mammogram were asked to participate. They were included in a prospective follow-up study concerning QoL in women with early-stage BC, and the influence of surgery and personality on QoL. This study was approved by the Medical Ethics Board of the St. Elisabeth Hospital as primary research institute.

Up to January 2007, 609 women were included, of whom 385 had an abnormal screening mammogram. Eventually 152 of these 385 women were diagnosed with breast cancer (BC group), whereas 233 women had a false-positive mammogram and were diagnosed with benign breast disease after investigation (FP group). All women gave written informed consent before entering the study.

Methods

Two-view mammography was used at initial breast screening, whereas subsequently only a medio-lateral view was taken. Two radiologists trained in screening mammography reviewed the mammograms separately. All women with a mammographic abnormality (positive screening) were referred to the surgical outpatient clinic. A positive test was classified as true positive if BC was diagnosed subsequently on the basis of pathological findings after biopsy. A test was classified as a false-positive if no pathological evidence of BC was found.[10]
Negative effects from screening were defined as all unwanted side-effects (physical, psychological, and economic) from the BC program. The present study focused on the diagnostic procedures (mammography, stereotactic and ultrasound-guided biopsy, and excision biopsy), number of outpatient visits, QoL, and anxiety.

Questionnaires

QoL was assessed using the World Health Organization Quality of Life assessment instrument 100 (WHOQOL-100)[11], a cross-cultural generic multi-dimensional questionnaire. This assessed QoL in six domains (Physical health, Psychological health, Level of independence, Social relationships, Environment and Spirituality) and a general evaluative facet (Overall QoL and general health). The reliability and validity of the instrument are good for women with breast disease.[12]
Personality was assessed at baseline using the Neuroticism-Extraversion-Openness-Five Factor Inventory (NEO-FFI)[13], and the trait anxiety scale of the State and Trait Anxiety Inventory (STAI).[14]
The NEO-FFI was developed to study an individual's personality. Personality is assessed in the five domains of the five-factor-model: neuroticism, extraversion, openness, agreeableness and conscientiousness. The psychometric properties are good.[13]
The STAI was originally developed to investigate anxiety phenomena in normal adults, but has also proven useful in medical and surgical patients. It measures two types of anxiety. Trait anxiety, assessed in the present study at baseline, concerns differences in individuals in the way they respond to stressful situations. State

anxiety was assessed at each measurement and refers to the amount of stress experienced at the moment of measurement. The psychometric characteristics of this questionnaire are well established.[14]
Patients were also asked to complete questions concerning demographic factors such as age, marital status, education, and socioeconomic status. Clinical data were obtained from the medical records.

Statistical procedures

One-way ANOVA, t-tests, and chi-square tests were used to compare baseline characteristics in the BC and FP groups. The predictors of overall QoL (dependent variable) one, three, six and twelve months after diagnosis were found using the demographic (block 1), clinical (block 2), and personality characteristics (block 3) as independent variables in multivariable regression analysis. Variables that significantly influenced overall QoL were then dichotomized (high score or not) and subsequently entered into logistic regression analysis to provide the odds ratio for a low overall QoL score.
A general linear model for repeated measures (GLM) was used to examine scores on overall QoL and state anxiety over time in both BC group and the FP group, and also according to trait anxiety in combination with the result of the screening mammogram (BC or FP). In each analysis the characteristics on which the groups appeared to differ at baseline were used as co-variables. Eta squared is an effect size that can be derived from the output of the GLM. An eta squared value between 0.01 and 0.06 denotes a small effect, between 0.06 and 0.13 a moderate effect, and 0.14 or higher a large effect.[15] To reach a statistical power of 0.80, at least 55 women were needed in each group, based on an expected moderate effect size. When differences were found in the GLM between groups, one-way ANOVA was used to examine QoL differences between groups at one particular measurement time. Again the characteristics on which the two groups differed at baseline were incorporated in the analyses as co-variables. A p-value < 0.05 was considered statistically significant. All analyses were performed with the Statistical Package for Social Sciences® version 16.0 (SPSS, Chicago, Illinois, USA).

Results

At baseline, before the abnormality on the screening mammogram was defined as either BC or FP, the two patient groups differed in age, with those in the FP group being significantly younger (mean age 57 versus 60 years; p<0.001). Other demographic characteristics were comparable (Table 1). The mammographic abnormality was significantly larger in the BC group (mean 17.4 versus 9.9 mm; p<0.001). There were no significant differences in personality between the two groups; however, scores on state anxiety at baseline were significantly different, with the BC group expressing more anxiety (mean 48.3 versus 40.1; p<0.001).

Table 1 Demographic, personality, and psychological characteristics in women with a mammographic abnormality: breast cancer (BC) or false-positive (FP)

	BC N=152	**FP N=233**	**P**
Demographics			
Age (years) *	60.2 (7.1)	57.3 (6.9)	**<0.001**
Partner	122 (82.5)	200 (87)	0.288
Children	117 (77)	170 (73.3)	0.556
Education (years) 0-10 10-14 >14	 61 (40.3) 62 (41.2) 25 (16.7)	 98 (42.2) 95 (40.9) 35 (15.1)	0.962
Tumour size on radiology (mm) *	17.4 (13.8)	9.9 (10.6)	**<0.001**
Personality			
Neuroticism *	30.0 (7.2)	31.1 (6.6)	0.133
Extraversion *	40.8 (5.4)	39.7 (5.6)	0.720
Openness *	35.6 (6.0)	36.6 (5.1)	0.086
Agreeableness *	43.9 (4.1)	43.5 (4.1)	0.389
Conscientiousness *	45.7 (5.4)	45.4 (4.7)	0.562
Trait anxiety *	39.6 (11.2)	38.4 (10.6)	0.318
Psychological factors			
Quality of life *	15.6 (2.4)	15.6 (2.6)	0.733
State anxiety *	48.3 (13.9)	40.1 (12.9)	**<0.001**

Values in parentheses are percentage unless indicated otherwise. * values are mean (s.d.).
Significant p-value presented in bold.

Significantly more diagnostic procedures (including biopsies) were needed in the FP group to reach a final diagnosis (p<0.001). In the BC group 130 patients (86 per cent) required three diagnostic procedures, and 14.5 per cent required four. In the FP group 75 patients (32 per cent) required more than three procedures. Only 66 women (29 per cent) in the FP group could be reassured after a repeat mammogram; all other women needed at least one core biopsy and in 18 (8 per cent) ultimately needed excision biopsy to arrive at the diagnosis.

Table 2 Quality of life and state anxiety for women with an abnormal mammogram over time since diagnosis

	Quality of life		**State Anxiety**	
	BC	**FP**	**BC**	**FP**
Baseline	16.0 (2.4)	15.2 (3.1)	48.1 (14.8)	39.0 (11)
1 month	15.4 (2.6) *	15.5 (2.8)	37.0 (11.1) *	33.4 (10.0) *
3 months	15.7 (2.5)	15.2 (3.0)	36.6 (12.8)	35.0 (11.1)
6 months	15.7 (2.5)	15.4 (2.8)	35.7 (12.7)	33.3 (11.5)
1 year	15.9 (2.5)	15.3 (2.8)	35.4 (11.5)	33.4 (10.9)

Values are mean (s.d.). BC = breast cancer group; FP = false-positive group. Overall, quality of life and state anxiety values were higher in the BC than in the FP group (both p<0.001); * p<0.001 versus baseline.

Table 3 Regression analyses for overall quality of life of women with an abnormal mammogram

	Patient group	**Independent factor**	**R^2**	**Beta**	**P**
1 month	FP	Trait anxiety	0.43	-0.656	<0.001
	BC	State anxiety Neuroticism	0.32 0.07	-0.566 -0.291	<0.001 0.006
3 months	FP	Trait anxiety State anxiety	0.55 0.04	-0.743 -0.291	<0.001 0.001
	BC	State anxiety Neuroticism	0.44 0.06	-0.666 -0.287	<0.001 0.003
6 months	FP	Trait anxiety State anxiety Extraversion	0.48 0.07 0.02	-0.689 -0.390 0.141	<0.001 <0.001 0.045
	BC	State anxiety Neuroticism	0.46 0.05	-0.676 -0.255	<0.001 0.006
1 year	FP	Trait anxiety	0.40	-0.679	<0.001
	BC	State anxiety Neuroticism	0.34 0.06	-0.585 -0.285	<0.001 0.012

BC = breast cancer group; FP = false-positive group. R^2 = the proportion of variance in the scores of the dependent variable explained by the independent variable (1.00 = 100%); a negative Beta value means that a higher score for the independent variable will result in a lower score for the dependent variable.

After the diagnosis, 105 women (45 per cent) in the FP group did not need (or want) a follow-up; 100 (43 per cent) came only once to the outpatient clinic in the following year and the remaining 28 came up to eight times.

There was a significant reduction in QoL between baseline and the measurement one month after diagnosis and surgery in the BC group. The scores on state anxiety were significantly reduced for both the FP and the BC groups between baseline and one month later (Table 2). Scores on state anxiety also differed significantly between the two groups at baseline and one month after surgery, with the BC group scoring higher (more anxious).

Regression analyses showed that the factors influencing QoL scores differed between the two patient groups. In the FP group, trait anxiety was the most important factor; it explained up to 55 per cent of the variance in QoL scores. In the BC group, neuroticism and state anxiety were the two significant influencing factors; neuroticism was responsible for up to 7 per cent of the effect, whereas state anxiety explained up to 46 per cent of the variance in scores (Table 3).

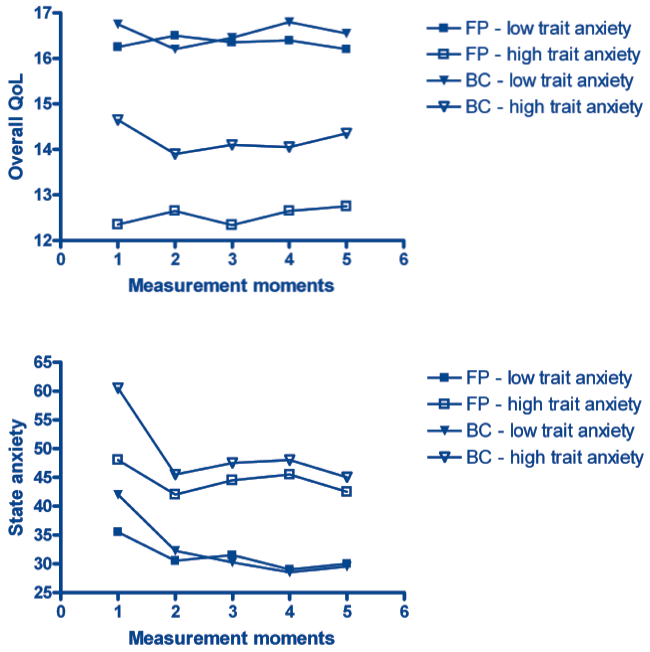

Figure 1 Overall quality of life and anxiety levels (general mean scores) in patients with breast cancer (BC) or a false-positive screening mammogram (FP) according to the level of personality characteristic trait anxiety at time intervals after diagnosis
Measurement moments: 1 = baseline, 2 = 1 month, 3 = 3 months, 4 = 6 months, 5 = 12 months.

When the women were divided into four groups based on the diagnosis (FP or BC) and their scores on the personality characteristic trait anxiety (high or low), it was found that the women with a high trait anxiety scored significantly lower on QoL and higher on state anxiety, irrespective of the diagnosis ($p<0.001$; Fig. 1). The Eta squared value for QoL was 0.27 and for state anxiety was 0.44. Although Figure 1 suggested a significant difference in QoL between the FP and BC groups with high trait anxiety scores, this was not confirmed in separate analyses.

Discussion

Discussion concerning the benefits and harms of BC screening is ongoing.[16,17] Some women truly benefit from early detection, whereas others experience harm and unnecessary anxiety. Thus, the decision to participate in a screening program requires balanced information about its potential benefits and dangers.[2,18]

In this study women scored high on state anxiety before diagnosis was known. One month after diagnosis, state anxiety reduced both in the women who turned out to have a false-positive mammogram and in those diagnosed with BC. The absolute decrease in scores was higher in the BC group. However, state anxiety was still the most important factor influencing overall QoL scores in the BC group. It was responsible for up to 46 per cent of the variance in scores. In the FP group, personality, and particularly the personality characteristic trait anxiety, was the most significant factor influencing overall QoL. Thus, anxious women fared worse after a false-positive result, an effect that lasted for at least one year after the screening mammogram.

In the Netherlands the recall rates after screening vary from 0.89 to 1.12 per cent.[5] This is very low in comparison with screening programs in other countries, which have reported recall rates of 2-5 per cent.[5,19] After recall, 60.5 per cent of the women were diagnosed with benign breast disease in the present study.

Factors that affect the risk of a false-positive mammogram result in general are the frequency of screening tests and fear of litigation; some authors in the United States estimate the risk of a false-positive test to be almost 50 per cent for women undergoing ten tests in 10 years.[8]

In a recent study it was calculated that women aged 50-51 years had a cumulative risk of 21 per cent for a false-positive recall with biannual screening over two decades.[20] Another study found that, for every 1000 women screened over 10 years, up to 25 per cent received an abnormal result, with 6.5 per cent of these women undergoing at least one biopsy.[21] In the present study 66 women (29 per cent) needed only a repeat mammogram, whereas 167 (72 per cent) underwent at

least one core biopsy and 18 women (8 per cent) eventually needed an excision biopsy to achieve a benign diagnosis.

In the information leaflet that is included with the invitation for BC screening it is mentioned that about 60 per cent of the women who are recalled will have a benign diagnosis. This value has been included in the information only since 2006. However, the diagnostic (sometimes invasive) procedures needed to reach this diagnosis are not mentioned either in the information leaflet or on the internet information site. In particular, there is no reference to any negative psychological effects this process may have.

Several studies have reported that most women with a false-positive result were glad they had been tested, felt that they were at high risk, and intended to be tested again.[2,22,23] Most of the fear caused by the positive test was removed by the result of the confirmatory tests. However, in that study the participants were interviewed by telephone and the questionnaires were completed some time after the women had been informed of the final diagnosis. Only one study reported concern during the year after the mammogram, with subsequent outpatient visits.[24] In the present study 55 per cent of the FP group returned to the outpatient clinic in the first year after the screening, some up to eight times. Some of these visits were requested by the treating physician, but many follow-up visits were instigated by the women themselves. The visits requested by a doctor might have influenced the QoL and state anxiety; however, with the exception of overall QoL six months after diagnosis, no differences were found between women who visited the outpatient clinic and women who did not, in terms of overall QoL and state anxiety (data not shown). This implies that the anxiety and lower QoL experienced by women with a false-positive mammogram were solely due to the recall after screening and the subsequent diagnostic procedures.

Women often overestimate their risk of BC and the benefits of screening, and are not aware of the possible dangers.[25] The material provided by professional groups and governmental institutions is often in favour of screening and not always objective. A cross-sectional study of 27 websites by interest groups in different countries found that the most important dangers of screening – overdiagnosis and overtreatment – were underexposed subjects.[26]

Women deserve more balanced information to help them chose whether or not to accept the invitation for screening mammography. This should not only focus on the supposed benefits, but should include potential side-effects such as increased feelings of anxiety.

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Chapter 3

Anxiety after an abnormal screening mammogram is a serious problem

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Abstract

Background
The aim of this study was to analyse the possible negative psychological consequences of a false-positive screening mammogram. We compared anxiety evoked by first time (FSM) versus repeat screening mammogram (RSM).

Methods
Between September 2002 and January 2010 women with an abnormality on a screening mammogram were included in our study. Questionnaires examining trait and state anxiety, depressive symptoms and quality of life (QoL), were completed prior to the diagnosis and during follow-up until 12 months.

Results
No differences in anxiety, depressive symptoms, and QoL were found between FSM (N=186) or RSM (N=296) groups. All women experienced high anxiety before diagnosis was known. High trait anxiety was predictive for more anxiety, depressive symptoms, and lower QoL. Women with low score on trait anxiety were more momentary anxious in FSM group compared with RSM group (p=0.048).

Conclusions
Negative psychological consequences after a false-positive screening mammogram are seen in *all* women. These effects are strengthened by personality and timing of the screening mammogram. All women should receive correct information concerning the negative psychological effects and should be offered psychosocial support if needed.

Introduction

Breast cancer (BC) screening is likely to reduce BC mortality, a reasonable estimate is a 15 per cent relative reduction or a 0.05 per cent absolute reduction.[1] However, the adverse consequences of screening such as false-positive findings are the reason for the ongoing debate whether the advantages of the screening program outweigh the disadvantages.[1]

In the Netherlands, the attendance rate of the BC screening program is approximately 80 per cent. The recall rate is 1 per cent, with an overall cancer detection rate of 5.1 per 1000 women.[2,3,4] The percentage of women with at least one false-positive result after a screening mammogram every two years is estimated to be 49 per cent after ten mammograms in the United States.[5] Women who receive false-positive results after a screening mammogram report more anxiety and distress in general and specifically concerning the possibility of having BC.[1,6-11] Even though this level of anxiety diminishes after the diagnostic process is completed, a significant amount of women with the diagnosis benign breast disease is not completely reassured.[12,13] Also, women with benign breast disease undergoing breast biopsy or fine needle aspiration report higher levels of stress and anxiety before biopsy and still several months after the additional investigations.[14,15] A decrease in quality of life (QoL) with an increase in anxiety was also seen in women undergoing additional investigations after an abnormal screening mammogram.[12] A recent review confirmed this impact of BC screening on QoL.[16] Anxious women again experience adverse psychological consequences just before being invited for their next breast screening appointment.[17,18] A recent review reported several possible factors predictive for psychological outcomes after a false-positive mammogram. The factors associated with more negative psychological outcomes were younger age, lower level of education, more anxious at the previous screening round, and a previous false-positive mammogram.[6]

The aim of this study was to analyse the possible negative psychological consequences of the screening mammogram program and the impact of these psychological consequences on QoL. We were especially interested in the timing of the screening mammogram. We hypothesized that when women attend the screening program for the first time and are referred because of an abnormal mammogram they may express more anxiety and depressive symptoms and experience a more pronounced decrease in QoL compared with women who have attended the program before without any problems and are thus ‘more experienced’. As previously shown, these effects are expected to be negatively influenced by personality, i.e. trait anxiety.[12] Contrary to most studies concerning

this subject, in this prospective, longitudinal study women completed the first set of questionnaires before any diagnostic procedures were performed.

Patients and methods

Screening

Since 1990 in the Netherlands BC screening is offered every two years to women in the age between 50 and 75 years. Every year one million women receive an invitation for BC screening mammogram. The overall attendance rate is 80 per cent.[4]

Participants

In the period between September 2002 and January 2010 women with an abnormality on a screening mammogram referred to the St. Elisabeth Hospital, the Maasland Hospital, the Jeroen Bosch Hospital, the Catharina Hospital, the Viecuri Medical Center, or the Medical Center Alkmaar (The Netherlands) were invited to participate in our study.

Two-view mammography was used at initial BC screening. All women with an abnormal screening mammogram were referred to the surgical outpatient clinic. A positive screening mammogram was classified as true positive if BC diagnosis was confirmed with biopsy. A false-positive screening mammogram was defined as true negative if the mammogram and/or ultrasound of the breast and/or biopsy were excluding the diagnosis BC.

The present study is part of a larger study focusing on the impact of personality and QoL on morbidity, mortality, and health care consumption in women with BC and benign breast disease. Women with recurrent benign breast disease or BC, poor expression of the Dutch language, or a (history of) psychiatric illness were excluded.

Procedure

Approval of the study protocol was given by the Medical Ethical Committee of the primary research hospital, being the St. Elisabeth Hospital. When women were invited to participate in the study and completed the first set of questionnaires, no additional diagnostic procedures were done yet and the diagnosis was still unknown. All participants gave written informed consent.

Questionnaires

Questionnaires were completed at baseline before diagnosis is known, and one, three, six and twelve months after the definitive diagnosis. The questionnaires used assessed personality (NEO-FFI, STAI-Trait), depressive symptoms (CES-D), momentary anxiety (STAI-State) and QoL (WHOQOL-Bref).

The Neuroticism-Extraversion-Openness-Five Factor Inventory (NEO-FFI) is developed to assess the Five Factor Personality Model: neuroticism, extraversion, openness to new experiences, agreeableness and conscientiousness.[19,20] The psychometric properties are good.[19] In the present study the questionnaire was completed at baseline and only the 12-items for neuroticism were used for the analyses. A high score for neuroticism was defined as a score above 38 in concordance with the manual.[19]

The State and Trait Anxiety Inventory (STAI) measures trait and state anxiety.[21,22] Trait anxiety concerns differences in individuals in the disposition to respond to stressful situations with varying amounts of stress. State anxiety is a momentary emotional condition characterized by subjective feelings of apprehension and tension, and heightened autonomic nervous system activity. This may vary in intensity and fluctuate over time.[21] The short version of the STAI-Trait and STAI-State was used.[23,24,25] The 6-items state scale was assessed at all measurement moments and the 10-items trait scale at baseline. High trait anxiety was defined as a score above 22, and high state anxiety was defined as a score above 14 according to the recommendations in the manual. The psychometric characteristics of this short version are well established and considered good.[23,24,25]

The Center for Epidemiological Studies-Depression Scale (CES-D) was used to assess depressive symptoms at all measurement moments. It measures both the presence and the degree of depressive symptoms with a 16-items scale. The reliability and validity appear to be good.[26,27]

The World Health Organization Quality of Life assessment instrument-Bref (WHOQOL-Bref) is a generic, cross-culturally developed comprehensive measure of QoL. It is the short version of the WHOQOL-100 questionnaire.[28,29] The WHOQOL-Bref measures QoL in four domains (Physical health, Psychological health, Social relationships and Environment) and the facet Overall QoL and general health. The psychometric properties of the WHOQOL-Bref are good in women with benign breast disease.[30] The WHOQOL-Bref was completed at two moments: at baseline and after 12 months.

At baseline, women were also asked to complete a questionnaire concerning demographic characteristics, such as age, paid work, children, marital status, and

education. The medical data concerning patient and mammogram characteristics were obtained from the medical records.

Statistical procedures

For examining differences between the two groups, first screening mammogram (FSM) or repeat screening mammogram (RSM), with regard to baseline personality and demographic characteristics chi-square tests and t-tests were used.
General linear model for repeated measures was used to examine scores on state anxiety, depressive symptoms, and QoL over time (i) in the two groups FSM and RSM, and (ii) in patients with a high or not-high score on trait anxiety in the FSM and RSM groups.
The predictors for state anxiety (dependent variable), depressive symptoms (dependent variable) and overall QoL (dependent variable) were found using the demographic (block 1) and personality characteristics (block 2) as independent variables in a multivariate linear regression analysis.
A p-value < 0.05 was considered statistical significant. All analyses were performed with the Statistical Package for Social Sciences® version 15.0 (SPSS, Chicago, Illinois, USA).

Results

In total 818 women were referred after an abnormal screening mammogram, in 527 (64 per cent) women benign breast disease was diagnosed. In 188 women with an abnormal result it was their first screening mammogram. In 30 women the timing of the screening mammogram was not known. Therefore, these women were excluded. At baseline, 15 of the 527 women did not fully or correctly complete the questionnaires and were excluded from further analysis.
At baseline there were no differences between the FSM group (N=186) and the RSM group (N=296) concerning demographics and personality, except for paid work and age. In the FSM group more women had paid work ($p<0.001$) and women in the RSM group were older ($p<0.001$; Table 1).
State anxiety scores showed the same pattern in the FSM and RSM groups. Both groups scored high before diagnosis and these scores significantly diminished after one, three and six months compared with baseline scores ($p<0.001$; Fig. 1).
Concerning depressive symptoms in the FSM and RSM groups a similar pattern was seen. Women scored high on depressive symptoms before diagnosis. These scores significantly decreased after one, three and six months in both groups ($p<0.001$). Again no differences were found between the groups.

When the women were divided in four groups based on first or repeat screening mammogram and their scores for trait anxiety at baseline (high versus not-high), it was found that women with a high score on trait anxiety (N=115) scored higher on state anxiety at baseline and during follow-up, irrespective of the group they were in (FSM or RSM) (p<0.001; Fig. 2). Women in the FSM group with a score not-high on trait anxiety (N=141) scored significantly higher on state anxiety at baseline compared with the RSM group not-high on trait anxiety (N=226), 12.5 versus 11.7 respectively (p=0.048). Women with a high score on trait anxiety were compared with women with a normal score with regard to demographics. A lower level of education was more often seen in women with high trait anxiety (p=0.001). With regard to depressive symptoms women with a high score on trait anxiety scored higher on depressive symptoms at all measurement moments, irrespective of the moment of the false-positive mammogram (p<0.001; Fig. 3).

Table 1 Demographic, personality and psychological characteristics at baseline for first (FSM) or repeat screening mammogram (RSM)

	FSM N=186	**RSM N=296**	**P**
Demographics			
Age (years) *	50 (0.8)	61 (5.9)	**<0.001**
Partner	163 (88)	254 (86)	0.145
Children	158 (85)	275 (93)	0.082
Education low/moderate	156 (84)	248 (84)	0.345
Paid work	141 (76)	106 (36)	**<0.001**
Personality			
Trait anxiety score *	18.0 (5.4)	18.2 (5.3)	0.663
High trait anxiety	45 (24)	70 (24)	0.856
Neuroticism score *	28.5 (7.5)	29.2 (6.8)	0.301
High neuroticism	12 (6)	28 (9)	0.216
Psychological factors			
State anxiety *	13.3 (4.0)	12.8 (4.2)	0.209
Quality of life *	7.7 (2.7)	7.8 (2.4)	0.634
Depressive symptoms *	8.9 (8.5)	9.0 (8.4)	0.836

Values in parentheses are percentage unless indicated otherwise. * values are mean (s.d.). Significant p-value presented in bold.

Figure 1 and 2 State anxiety per diagnosis and per diagnosis and score on trait anxiety
FSM = first screening mammogram, RSM = repeat screening mammogram, NHTA = not-high trait anxiety, HTA = high trait anxiety

Fig. 1

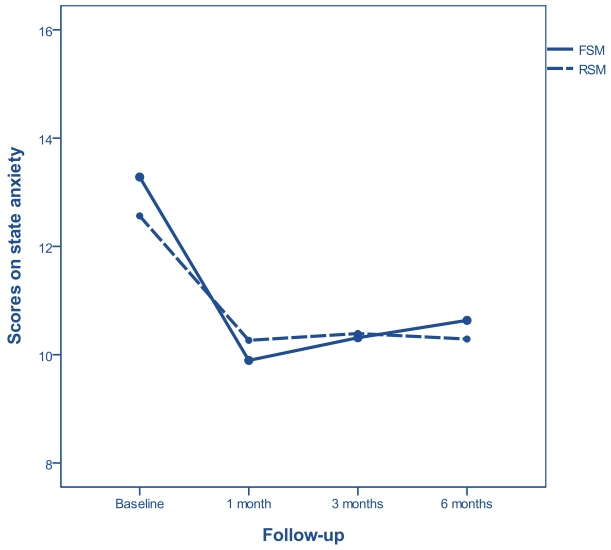


Fig. 2

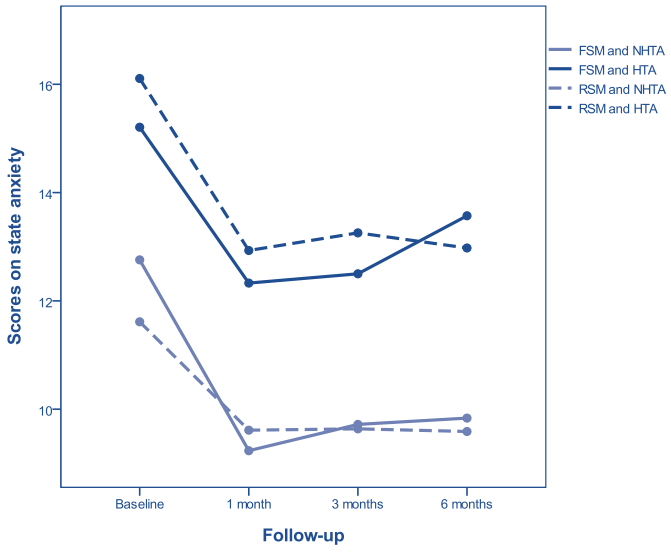


Figure 3 and 4 Depressive symptoms and quality of life per diagnosis and score on trait anxiety FSM = first screening mammogram, RSM = repeat screening mammogram, NHTA = not-high trait anxiety, HTA = high trait anxiety

Fig. 3

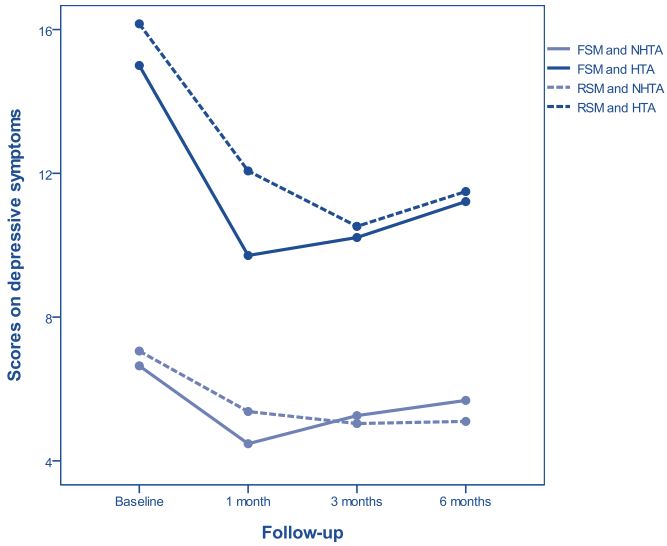
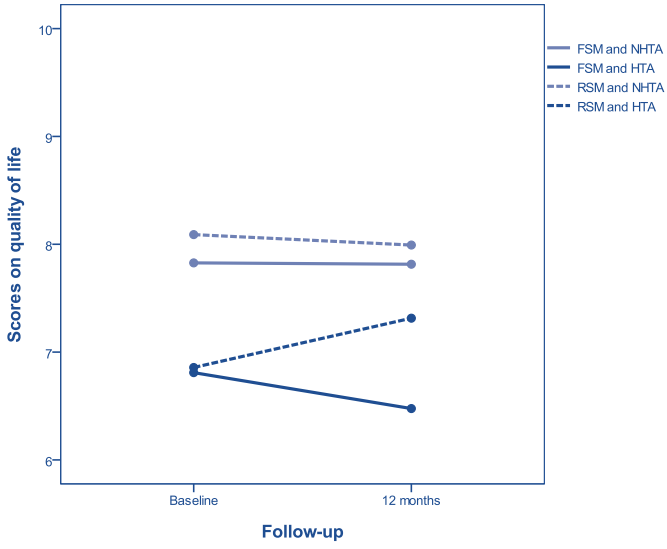


Fig. 4



Concerning the scores of the four domains QoL and the overall QoL there were no differences between the FSM and the RSM groups found at baseline and at 12 months follow-up. Women in the FSM group who did not score high on trait anxiety scored lower on the domain social QoL compared with the women who did not score high on trait anxiety in the RSM group (p=0.047). Scores on overall QoL and the four domains QoL were consistently lower in women with a high score on trait anxiety in both groups at baseline (p<0.001) and at 12 months (p=0.015; Fig. 4). Regression analyses revealed that the most important factor of influence was trait anxiety in both groups considering state anxiety and depressive symptoms and QoL. In the FSM group other factors of influence were neuroticism, age and marital status and in the RSM group those factors were neuroticism, paid work and education, but their influence was small compared with the impact of trait anxiety (Table 2).

Table 2 Regression analyses for state anxiety, depressive symptoms and quality of life (QoL) as dependent variables

Measurement moment	Patient group	Independent factor	R^2	Beta	P
State anxiety 6 months	FSM	Trait anxiety	0.18	0.419	<0.001
State anxiety 6 months	RSM	Trait anxiety Paid work Neuroticism	0.17 0.03 0.02	0.342 0.173 0.169	<0.001 0.006 0.015
Depressive symptoms 6 months	FSM	Trait anxiety Neuroticism	0.09 0.03	0.240 0.180	0.009 0.049
Depressive symptoms 6 months	RSM	Trait anxiety Neuroticism Paid work	0.12 0.05 0.03	0.244 0.240 0.127	0.001 0.001 0.047
Psychological domain QoL 12 months	FSM	Trait anxiety	0.23	-0.479	<0.001
Psychological domain QoL 12 months	RSM	Trait anxiety Paid work Education Neuroticism	0.07 0.04 0.04 0.02	-0.214 -0.190 0.154 -0.167	0.009 0.013 0.044 0.040

FSM = first screening mammogram; RSM = repeat screening mammogram. R^2 = percentage of variance in the scores of the dependent variable explained by the independent variable (1.00 = 100%); Beta: a negative Beta means that a higher score on the independent variable will result in a lower score of the dependent variable.

Discussion

The adverse psychological consequences caused by false-positive findings after a screening mammogram are an important reason for the ongoing debate concerning the BC screening program.[1] Therefore, it is important not only to inform women properly concerning pro's and con's of screening but also to identify those women at risk for adverse psychological consequences after a false-positive mammogram.

The aim of the present study was to analyse the effect of the timing of an abnormal screening mammogram (first time versus repeat mammogram). A difference in anxiety, depressive symptoms, and QoL in favor of women with previous experience with screening mammograms was expected. Also, an influence of trait anxiety and neuroticism was expected. In our study no significant differences were observed between the two groups (FSM and RSM) on anxiety, depressive symptoms or QoL. All women experienced high anxiety before diagnosis was known.

However, when women were divided into four groups based on timing of the mammogram and their scores on the personality characteristic trait anxiety a significant difference in state anxiety was found. Women in the FSM group who were not prone to anxiety did respond with more anxiety after a false-positive mammogram. Apparently these women are insufficiently prepared for the possibility of a false-positive mammogram. Women not prone to anxiety who had experience with the screening program did experience lower levels of anxiety.

A high score on trait anxiety correlated significantly with high scores on state anxiety and depressive symptoms, irrespective of the experience of the woman with the screening program. Concerning neuroticism a similar pattern was seen for state anxiety, depressive symptoms and QoL as for trait anxiety. Almost all women with a high score on neuroticism scored high on trait anxiety. Anxiety can be considered as a part of the domain neuroticism, but can also be defined individually. Therefore, the same effects seen in women scoring high on neuroticism and trait anxiety can be explained by the correlation between neuroticism and anxiety. It is known that women's daily activities and QoL are affected by the higher levels of anxiety.[16]

It is possible that our results are an underestimation. Women with a high score on trait anxiety at baseline were more frequently not able to complete all questionnaires during follow-up. Therefore, we can assume that our results would have been even more convincing if those women had returned all questionnaires.

This present study confirms previous findings in which women with a false-positive screening mammogram experienced for at least one year a low QoL and feelings

of anxiety, especially when they score high on trait anxiety.[12] The present study is performed in more hospitals (six versus three) and more women were included (482 women versus 233 women) than in our previous study. Therefore, we can conclude that the previous results are validated by this study. Contrary to most studies concerning this subject, in our study the first questionnaires were completed before diagnosis was known, which makes our results even more consistent.

In the Netherlands, annually around 900.000 women undergo a screening mammogram with a recall rate of 1 per cent and a false-positive rate of 66 per cent.[4] Concerning the comparable false-positive rate of 64 per cent in our study group with 115 women (24 per cent) scoring high on trait anxiety, these rates imply a large group of women who are at risk for adverse psychological consequences. In the United States the recall rate is 11 per cent after a first screening mammogram and 7 per cent after a subsequent screening mammogram.[31] Concerning this higher recall rate compared with the Dutch situation, adverse psychological consequences after a false-positive screening mammogram are expected to be an even more serious problem in the United States.

Recently several publications have been addressing the screening controversy by questioning the benefits and harms of the BC screening program.[1,32-38] The decision to participate in the BC screening program is based upon information in favor of screening without mentioning the risk for overdiagnosis and overtreatment and the possible adverse psychological consequences.[1,35-37,39,40] In the present study these adverse psychological consequences are confirmed. The levels of anxiety found in chronically anxious women were in 79 per cent abnormal (with a score above 14), whereas in 30 per cent of the women without high trait anxiety abnormal anxiety scores were found (data not shown).[23] Therefore, this high anxiety cannot be considered as a normal response to screening, in the sense that not every woman responds with elevated anxiety. In addition, in our previous study 55 per cent of the women frequently visited the outpatient clinic in the first year after their false-positive screening mammogram.[12] Apparently, these women need more reassurance to confirm that their diagnosis is not BC. We recommend that every woman should be offered a psychometric test at the time of recall after an abnormal screening mammogram. Those women with high state anxiety should be offered psychosocial interventions that focus on learning how to cope with these stressful events.

Conclusions

This study reveals that the adverse psychological consequences after a false-positive screening mammogram are seen in *all* women. These effects are influenced by personality and by the timing of the screening mammogram. Women participating in the screening mammogram program should receive correct and complete information *every* screening round before they decide to participate. This information should mention the risk of experiencing adverse psychological consequences and every woman should be offered psychosocial support when necessary.

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Chapter 4

An abnormal screening mammogram causes more anxiety than a palpable lump in benign breast disease

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Abstract

Background

Being recalled for further diagnostic procedures after an abnormal screening mammogram (ASM) can evoke a high state anxiety with lowered quality of life (QoL). We examined whether these adverse psychological consequences are found in all women with benign breast disease (BBD) or are particular to women referred after ASM. In addition, the influence of the anxiety as a personality characteristic (trait anxiety) was studied.

Methods

Between September 2002 and February 2010 we performed a prospective longitudinal study in six Dutch hospitals. Women referred after ASM *or* with a palpable lump in the breast (PL), who were subsequently diagnosed with BBD, were included. Prior to diagnosis (at referral) and during follow-up, questionnaires were completed examining trait anxiety (at referral), state anxiety, depressive symptoms (at referral, one, three and six months after diagnosis), and QoL (at referral and 12 months).

Results

Women referred after ASM (N=363) were compared with women with PL (N=401). A similar state anxiety score was found in both groups, but a lower psychological QoL score at 12 months was seen in the ASM group. In women with not-high trait anxiety those in the ASM group were more anxious with more depressive symptoms at referral, and reported impaired psychological QoL at referral and at 12 months compared with the PL group. No differences were found between ASM and PL in women with high trait anxiety, but this group scored unfavorably on anxiety, depressive symptoms and QoL compared with women with not-high trait anxiety.

Conclusions

ASM evokes more anxiety and depressive symptoms and lowered QoL compared with women referred with PL, especially in women who are not prone to anxiety. Women should be fully informed properly about the risks and benefits of breast cancer screening programs. We recommend identifying women at risk of reduced QoL using a psychometric test.

Introduction

Breast cancer (BC) is the most common cancer among women. In the western world one in eight women is at risk of developing BC.[1,2] However, the majority of women visiting the surgical outpatient clinic with breast problems, such as a palpable lump (PL) or an abnormal screening mammogram (ASM), are diagnosed with benign breast disease (BBD).[3] During the investigation of breast symptoms, women experience increased anxiety and distress.[4-6] Even after a diagnosis of BBD is made, these symptoms persist in a proportion of women.[4] Women with BBD diagnosed after an ASM report ongoing anxiety[7-9] with lowered quality of life (QoL).[10,11] In chronically anxious women (i.e. with high trait anxiety) these psychological effects are heightened.[6,10,12] Trait anxiety refers to relatively stable individual differences in anxiety proneness.[13]

Thus, it is important to evaluate women diagnosed with BBD as the lack of reassurance after the diagnostic work-up and adverse psychological consequences may result in lowered QoL. Although these effects on women with BBD have been previously studied, a comparison between women referred after an ASM *or* with PL has not been performed before. This comparison is important in the context of the ongoing discussions on whether the advantages of a BC screening program still outweigh the disadvantages (such as the false-positive findings).[14,15] Therefore, we examined whether all women with BBD (ASM and PL) experience similar levels of anxiety (state anxiety), depressive symptoms, and changes in QoL during and in the year following the diagnostic work-up. Women attending BC screening usually have no palpable lump in the breast and so are not expecting an ASM. We hypothesized that these women are more alarmed by being recalled for further diagnostic procedures and experience more adverse psychological effects compared with women with a PL. Based on previous studies, we also analysed the influence of the personality characteristic trait anxiety.[10,16]

In this prospective, longitudinal study comparing ASM with PL, women completed the first set of questionnaires before any diagnostic procedures were performed (at referral).

Patients and Methods

Participants

Women referred after an ASM or with a PL were eligible for participating in this study. The study was conducted between September 2002 and February 2010 in six Dutch hospitals. The Medical Ethical Committee of the primary research hospital, i.e. the St. Elisabeth Hospital, Tilburg, approved the study protocol. This study was part of a larger study analysing the impact of personality and QoL on morbidity, mortality and health care consumption in breast disease. Women with recurrent BBD or BC, inability to read and write in Dutch, or (previous) psychiatric illness were excluded. When women were invited to participate in the study and completed the first set of questionnaires, the diagnosis was unknown. All participants gave written informed consent.

Since 1990, BC screening is offered every two years to women in the age between 50 and 75 years in the Netherlands. Every year one million women receive an invitation for BC screening mammogram. The overall attendance rate is 80 per cent.[17] Two-view mammography was used at initial BC screening. All women with an ASM were referred to a dedicated outpatient breast clinic.

Questionnaires

Questionnaires were completed at referral (before diagnosis was known), and one, three, six and twelve months after diagnosis. The questionnaires assessed personality at referral (STAI-Trait), experienced momentary anxiety (STAI-State) and depressive symptoms (CES-D) at referral until six months, and QoL (WHOQOL-Bref) at referral and 12 months after diagnosis.

The State and Trait Anxiety Inventory (STAI) measures two types of anxiety: trait and state. Trait anxiety refers to the tendency to respond to situations perceived as threatening with a rise in anxiety intensity. State anxiety refers to the amount of stress being experienced at the specific moment the measurement is made.[13,18] In this study, the short 6-items state version and 10-items trait version of the STAI were used.[19,20] High trait anxiety (HTA) was defined as a score greater than 22. The reliability and validity of the short versions are considered good.[19,20]

The Center for Epidemiological Studies-Depression Scale (CES-D) was used to assess depressive symptoms. It measures both the presence and the degree of depressive symptoms. The psychometric properties are good.[21,22]

The World Health Organization Quality of Life assessment instrument-Bref (WHOQOL-Bref) is a short version of the WHOQOL-100.[23,24] The WHOQOL-Bref consists of questions assessing QoL within four domains (Physical health, Psychological health, Social relationships and Environment) and a general

evaluative facet (Overall QoL and general health). The psychometric properties of the WHOQOL-Bref have been demonstrated to be good in women with BBD.[3] Women were also asked to complete a questionnaire concerning demographic characteristics. The medical data concerning patient and mammography characteristics were obtained from the medical records.

Statistical procedures

Women who did not complete all questionnaires during follow-up, were excluded from further analysis and considered as drop-outs. Chi-square tests and independent t-tests were used to compare women in the non drop-out and drop-out groups, and in the ASM or PL groups with regard to demographic (age, children, marital status, paid work, educational level) and personality (trait anxiety) characteristics at baseline. Differences in demographic characteristics were used as covariates in the subsequent analysis.

A repeated measures general linear model was used to examine scores on state anxiety and depressive symptoms (at referral until six months), and QoL (at referral and 12 months) across time (i) in the two groups ASM or PL, and (ii) in women with HTA or not-high score on trait anxiety (NHTA) in ASM or PL groups. A p-value < 0.05 was considered statistical significant. All analyses were performed with the Statistical Package for Social Sciences® (SPSS version 18.0).

Results

During the study period 1145 women were diagnosed with BBD. During follow-up, 381 women did not complete all questionnaires, and were excluded from further analysis. Women in the drop-out group were less educated ($p=0.016$) and scored higher on trait anxiety ($p<0.001$) compared with the group that remained in the study. There was no difference concerning referral after ASM or PL.

In total, 764 women were analysed at referral, 363 women in the ASM group and 401 in the PL group. At referral significant differences were observed concerning demographics between the two groups (Table 1). Women in the ASM group were older ($p<0.001$), more often had children ($p=0.009$), and less often had paid work ($p<0.001$). There was no difference between the two groups concerning trait anxiety at referral.

Table 1 Demographic and psychological characteristics comparing two groups: women with benign breast disease referred with an abnormal screening mammogram (ASM) or with a palpable lump in breast (PL)

	ASM N=363	PL N=401	P
Demographics			
Age (years) *	56.2 (6.8)	46.5 (10.9)	**<0.001**
Partner	308 (85)	348 (87)	0.315
Children	315 (88)	322 (81)	**0.009**
Education < 14 years	290 (80)	306 (76)	0.053
Paid work	194 (54)	289 (72)	**<0.001**
Personality			
High score on trait anxiety	75 (21)	85 (21)	0.856
Psychological factors			
State anxiety at referral *	12.9 (4.0)	12.4 (3.8)	0.074
State anxiety 6 months *	10.4 (3.4) °	10.4 (3.5) °	0.988
Depressive symptoms at referral *	8.8 (8.2)	7.2 (7.6)	**0.007**
Depressive symptoms 6 months *	6.5 (7.0) °	6.0 (7.1) °	0.407
General quality of life at referral *	7.9 (1.4)	7.9 (1.4)	0.732
General quality of life 12 months *	7.7 (1.4)	8.0 (1.4)	0.385

Values in parentheses are percentage unless indicated otherwise. * values are mean (s.d.). Significant p-value presented in bold. ° = scores diminished significantly at six months compared with scores at referral.

At referral, the mean scores for state anxiety were comparable in the ASM and PL groups (p=0.074; Table 1). In both groups, the state anxiety scores significantly decreased after one month compared with the scores at referral (p<0.001; Table 1). Concerning depressive symptoms, a higher mean score was found in ASM compared with PL at referral (p=0.007), in both groups scores significantly decreased at one month compared with the scores at referral (p<0.001; Table 1). After one month no differences between the two groups were found. From one month follow-up scores on state anxiety and depressive symptoms remained similar until six months in both groups (Table 1). Concerning the scores on QoL, there were no differences between the ASM and the PL groups at referral. At 12 months women in the ASM group scored lower on psychological QoL (p=0.022) compared with the PL group. In the subanalysis, women were divided in four groups based on referral after ASM or with PL and their scores on trait anxiety (HTA or NHTA).

High trait anxiety

Women with HTA (N=160) scored higher at all measurement moments on state anxiety, depressive symptoms, and lower on QoL compared with women with NHTA (p<0.001; Table 2). Within the group with HTA, women in the PL and ASM groups scored similar on state anxiety, depressive symptoms, and QoL (Table 2; Fig. 1 and 2). In both groups scores on depressive symptoms decreased significantly at one month compared with scores at referral (p<0.001). The only difference was a higher score on psychological QoL at referral in the ASM group (p=0.029).

Not-high trait anxiety

In women with NHTA (N=604), higher scores on state anxiety at referral were found in the ASM group compared with the PL group (p=0.047). During follow-up these scores significantly diminished after one month compared with the scores at referral in both groups (p<0.001; Table 2; Fig. 1), and the scores remained similar until six months compared with one month, without differences between groups. Scores on depressive symptoms were higher in ASM at referral compared with PL (p<0.001; Table 2; Fig. 2). In both groups scores after one month remained similar during follow-up. Concerning QoL women in the ASM group scored lower on psychological QoL at referral (p=0.022) and at 12 months (p=0.005) compared with the PL group.

Table 2 Scores at referral and during follow-up on state anxiety, depressive symptoms, and general quality of life (QoL) comparing four groups based on referral after abnormal screening program (ASM) or with palpable lump in breast (PL) and high trait anxiety (HTA) or not-high trait anxiety (NHTA)

	ASM N=75		**PL N=85**		**P**
HTA *	**At referral**	**6 months**	**At referral**	**6 months**	
State anxiety	15.7 (3.4)	13.1 (3.6)	15.5 (3.5)	13.2 (3.6)	NS
Depressive symptoms	15.8 (9.3)	11.4 (9.3) °	14.7 (9.6)	12.3 (8.8) °	NS
	At referral	**12 months**	**At referral**	**12 months**	
General QoL	6.9 (1.4)	6.9 (1.6)	6.7 (1.5)	6.7 (1.3)	NS
	ASM N=288		**PL N=316**		**P**
NHTA *	**At referral**	**6 months**	**At referral**	**6 months**	
State anxiety	12.2 (3.9)	9.7 (3.0) °	11.6 (3.4)	9.7 (3.1) °	B 0.047
Depressive symptoms	7.0 (6.8)	5.3 (5.6)	5.2 (5.4)	4.4 (5.4)	B <0.001
	At referral	**12 months**	**At referral**	**12 months**	
General QoL	8.1 (1.4)	8.0 (1.3)	8.2 (1.2)	8.3 (1.2)	NS

Values are mean (s.d.). NS = not significant. ° = scores significantly changed at six months compared with scores at referral. * = all values in the HTA groups are significant different compared with NHTA groups (p<0.001). B = significant difference at referral comparing ASM and PL.

Figure 1 and 2 State anxiety and depressive symptoms per diagnosis and score on trait anxiety
NHTA = not-high trait anxiety, PL = palpable lump, HTA = high trait anxiety, ASM = abnormal screening mammogram

Fig. 1

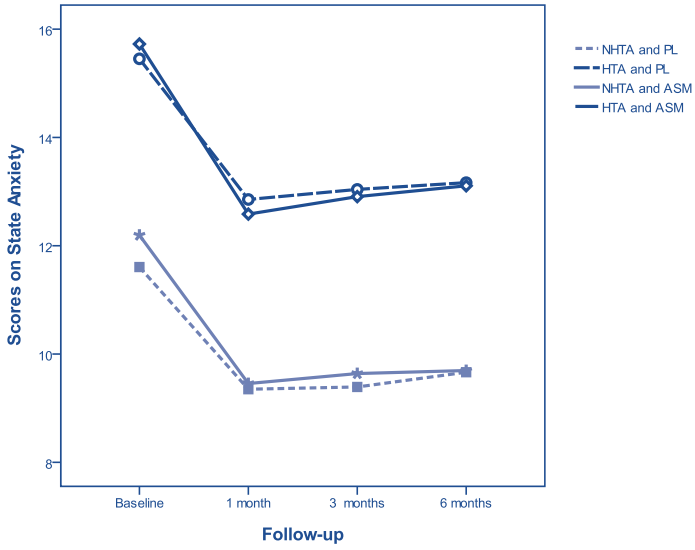
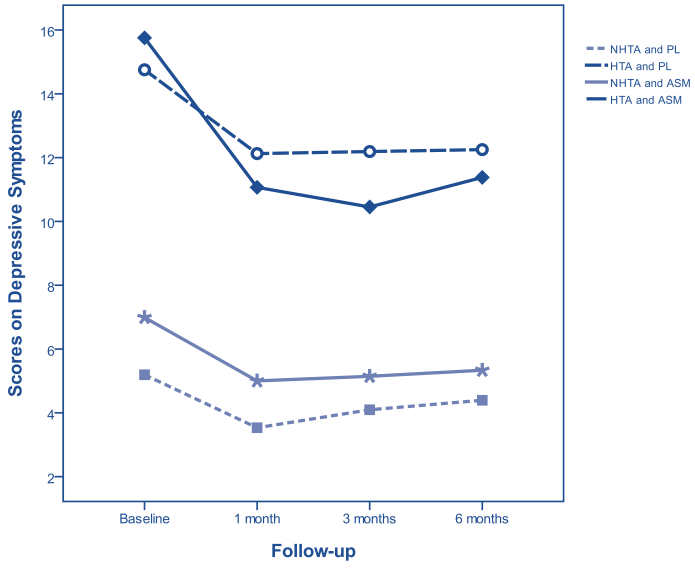


Fig. 2



Discussion

The discussion concerning the disadvantages of the BC screening program, such as false-positive findings, is still ongoing and contributing to the screening controversy.[14,15] The adverse psychological consequences after a false-positive screening mammogram are already described before.[7-11,16] However, to our knowledge, a comparison between women with BBD referred after ASM *or* PL has not yet been performed. We hypothesized that women referred after ASM experience more adverse psychological effects compared with women referred with PL.

As previously found, the negative effects in our study were strengthened by the personality characteristic trait anxiety, i.e. women with HTA scored unfavourably on state anxiety, depressive symptoms, and QoL, compared with women not prone to anxiety.[6,10,12] Before diagnosis was known, all women scored higher on state anxiety and depressive symptoms compared with one month after diagnosis, when women were relieved that BC was not found. In addition, we have found that within women not prone to anxiety, those in the ASM group were more anxious before diagnosis was known and experienced more depressive symptoms at referral compared with all women with PL. In addition, those women reported impaired psychological QoL at referral and one year after diagnosis compared with PL. In chronically anxious women higher scores on depressive symptoms at referral were found compared with one month after diagnosis, regardless of being referred after an ASM or with a PL.

Thus, the negative impact of a false-positive screening mammogram on anxiety, depressive symptoms and QoL is especially found in women who do not have a high propensity for anxiety, confirming our previous findings.[16] These effects cannot be considered as a normal response to the diagnostic work up for breast disease, because not every woman responds similar to the threat of possibly having BC. The fact that women not prone to anxiety are affected more implies that being recalled for further diagnostic procedures after an ASM is a serious psychological problem, especially because the adverse effects persist at least one year after the diagnostic process showed by the lowered QoL.

The present findings contribute to the ongoing screening controversy: are the advantages of the BC screening program still in balance with the disadvantages? Recent data has suggested that screening has little detectable impact on BC mortality.[25] In addition, several publications have discussed the benefits and harms of the BC screening program.[14,15,26-31] Currently the decision to participate in the BC screening program is based upon information in favor of screening. The risk for

possible adverse psychological consequences, overdiagnosis and overtreatment are not mentioned in the provided information.[14,28-30,32,33]

Conclusions

This study reveals that women recalled after an ASM experience higher state anxiety and depressive symptoms at referral with lowered QoL one year after diagnosis, compared with women with a PL, especially women not prone to anxiety. Therefore, we recommend that women should be informed properly concerning the benefits and risks of the BC screening program, in particular mentioning the adverse psychological consequences after a false-positive screening mammogram. In addition, at intake women should be offered a psychometric test to identify those who are at risk for impaired QoL.

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Chapter 5

Health care utilization one year following the diagnosis benign breast disease or breast cancer

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Abstract

Background

We analysed health care utilization (HCU) and its predictors in the first year after the diagnostic process for breast cancer (BC) or benign breast disease (BBD). The impact of trait anxiety on HCU was examined.

Methods

From June 2007 until October 2009 women referred with a palpable lump in the breast or an abnormality on a screening mammogram, were asked to participate. Questionnaires were completed before diagnosis was known and after one year. The questionnaires used assessed personality (STAI-Trait, NEO-FFI), depressive symptoms (CES-D), fatigue (FAS), and quality of life (WHOQOL-Bref). HCU was measured with self-report questionnaire.

Results

In total 591 women were analysed, 440 with BBD and 151 with BC. In women with BBD and high trait anxiety (HTA) increased HCU was found. In women with BC and HTA only more use of psychosocial care (PS) was found. HCU in BBD was predicted by lower quality of life (QoL) and (adjuvant) treatment predicted HCU in BC.

Conclusions

The most important factors for higher HCU were HTA and lower QoL, especially in BBD. In women with BC increased PS use was seen in chronically anxious women. Therefore, it is important to identify these women using a psychometric test and to anticipate to their specific (mental) health care needs.

Introduction

Nowadays, one in eight women in the western world will ultimately be diagnosed with breast cancer (BC).[1,2,3] However, in our experience, the majority of women presenting at the surgical outpatient clinic with breast symptoms or referred after an abnormal screening mammogram, are diagnosed with benign breast disease (BBD).[4] This large group of women is important to consider, because these women report increased levels of anxiety before and during the diagnostic process comparable with women with BC.[5-7] These levels of anxiety diminish after the diagnostic process is completed, but a significant amount of women with the diagnosis BBD are not completely reassured.[7,8]

A recent review revealed that trait anxiety was predictive for experienced levels of anxiety during the diagnostic process for suspected BC.[9] In addition, previous studies have shown that trait anxiety is not only an important predictor for anxiety, but also for quality of life (QoL) in women with BBD or BC.[4,7,10]

Trait anxiety refers to the tendency to respond to situations perceived as threatening with a rise in anxiety intensity.[11] Women who are chronically anxious tend to perceive new situations, for example a possible diagnosis BC, as threatening and therefore experience higher levels of anxiety. These higher levels of anxiety and lowered QoL could be reason for an increase in health care utilization (HCU) in women with BBD or BC, especially in those who score high on trait anxiety (HTA). However, limited research concerning HCU in women with BBD or BC is performed. A few studies examined which factors may contribute to increased HCU for BC patients only, resulting in the following predictors: younger age, breast amputation, co-morbidity, older age, not having a partner, radiotherapy, cancer-related health problems, depression, and breast reconstruction.[12-15]

We believe it is important to determine the patterns and the predictors of HCU in women with BBD or BD. With this knowledge about the medical and psychosocial needs of these women it will be possible to anticipate to those needs and eventually adjust the current follow-up protocol guidelines.

We evaluated the HCU and the predictors for HCU in women with BBD or BC during the first year following the diagnosis. A comparison in HCU was done between women with BBD or BC. Contrary to most studies concerning personality and QoL, in this prospective, longitudinal study women completed the first set of questionnaires before any diagnostic procedures were carried out and thus before diagnosis was known. Firstly, we hypothesized that women with HTA would have increased HCU in the first year after diagnosis, in both the BBD and the BC group.

Secondly, based on previous research and experience we expected that HCU was predicted by QoL, fatigue and depressive symptoms.

Patients and methods

Participants

The present study was performed in five teaching hospitals in the Netherlands. From June 2007 until October 2009 women referred with a palpable lump in the breast or an abnormality on a screening mammogram, were asked to participate in this study. The present study is part of a larger prospective, longitudinal study focusing on the impact of personality and QoL on morbidity, mortality and health care utilization in women with benign or malignant breast disease. At the time women gave written informed consent and completed the first set of questionnaires, the diagnosis was not yet known. If women were not able to complete Dutch questionnaires for linguistic or cognitive reasons, or if they had a medical history with BC or a psychiatric disease, they were excluded from the study. Women with advanced BC disease were excluded. The protocol of the study was approved by the local Medical Ethical Committee.

Health Care Utilization

HCU was divided in three major categories: visits to the general practitioner (GP), visits to the medical specialist (MD), and the use of psychosocial health care (PS), i.e. psychologist, welfare worker, self-help groups. After 12 months HCU was measured by self-report questions concerning visits and contacts with the GP, MD, and PS during the first year after diagnosis.

Questionnaires

Questionnaires were completed before any diagnostic procedures were carried out and thus before diagnosis was known. The questionnaires used assessed personality (STAI-Trait, NEO-FFI), depressive symptoms (CES-D), fatigue (FAS), and quality of life (WHOQOL-Bref).

Trait and state anxiety were measured with the State and Trait Anxiety Inventory (STAI).[11,16] Trait anxiety concerns differences in individuals in the disposition to respond to stressful situations with varying amounts of stress. State anxiety is a momentary emotional condition characterized by subjective feeling of apprehension and tension.[11,16] The trait anxiety scores were dichotomized in high or not-high. In this study the short forms of both the STAI-Trait and the STAI-State were completed. These short versions of the STAI-State (6-items) and STAI-Trait (10-items) have good reliability and validity.[17]

The personality trait neuroticism was measured by the neuroticism part (12-items) of the Neuroticism-Extraversion-Openness-Five Factor Inventory (NEO-FFI).[18,19] Neuroticism describes the predisposition to emotional instability, i.e. the tendency to experience no distressing emotions such as fear, guilt and frustration. The reliability and validity of this questionnaire are good.[18]
The Center for Epidemiological Studies-Depression Scale (CES-D) measures the presence and degree of depressive symptoms. The short version with 16-items was used, which was found to be a valid assessment of depressive symptoms in cancer patients.[20,21]
Fatigue was measured by the 10-items Fatigue Assessment Scale (FAS).[22] The reliability and validity of the FAS appears to be good in women with breast problems.[23]
The World Health Organization Quality of Life instrument, short form (WHOQOL-Bref) was used to assess QoL.[24] This questionnaire consists of four domains (Physical health, Psychological health, Social relationships and Environment) and two items concerning Overall QoL and general health. Higher scores indicate a better subjective QoL. Reliability and validity are reported to be good in women with breast problems.[25]

Demographical and medical information
Demographic data were obtained at baseline concerning age, marital status, having children, education level, and work status. Information on disease stage at diagnosis[26], type of operation, and adjuvant therapy (chemotherapy, radiotherapy, hormone therapy) was retrieved from patients' medical records.

Statistical procedures
For baseline measures, chi-square (discrete variables) and independent samples t-tests (continuous variables) were used to compare drop-outs and non-drop-outs. To examine differences in visits to the GP, MD and PS (i) in the groups BBD and BC, and (ii) in patients with HTA or not-high score on trait anxiety (NHTA) in the BBD and BC group, chi-square tests (discrete variables) and independent samples t-tests (continuous variables) were used.
Multivariate regression analyses were used to assess which factors were significant predictors of the number of contacts with the GP or MD and whether a patient used psychosocial health care in the first year following diagnosis. The independent variables included in the analyses were the following: demographics, disease stage, (adjuvant) therapy, personality, and baseline scores for state anxiety, depression, fatigue, and QoL domains. All analyses were performed with

the Statistical Package for Social Sciences® version 18.0 (SPSS, Chicago, Illinois, USA).

Results

During the study period 754 women were included, of whom 163 women did not complete all questionnaires after 12 months follow-up. Baseline demographics and personality were compared between drop-outs (N=163) and non-drop-outs (N=591): in the drop-out group more women were diagnosed with BBD, scored high on trait anxiety, and were less often referred by the national screening program.

Table 1 Demographics, personality, and treatment characteristics of women with benign breast disease (BBD) and women with breast cancer (BC)

	BBD N=440	**BC N=151**	**P**
Age (years) *	49.9 (10.5)	59.1 (9.2)	**<0.001**
Partner			
Yes	378 (89)	117 (79)	**0.003**
Children			
Yes	366 (84)	130 (86)	0.462
Educational level			
Low (< 10 years)	36 (8)	19 (13)	
Middle (11-14 years)	312 (72)	107 (71)	
High (> 14 years)	86 (20)	24 (16)	0.209
Work status			
Employed	307 (71)	56 (37)	**<0.001**
Screening referral ^			
Yes	173 (39)	103 (68)	**<0.001**
Personality			
Scores on trait anxiety *	16.9 (5.0)	18.1 (5.4)	**0.009**
High trait anxiety	72 (16)	42 (28)	**0.002**
Neuroticism	25 (6)	13 (9)	0.241
Disease stage at diagnosis			
Stage 0		13 (8)	
Stage I		82 (54)	
Stage IIa		34 (23)	
Stage IIb		10 (7)	
Stage III		12 (8)	
Type of operation			
Breast Conserving Treatment		108 (71)	
Mastectomy		42 (28)	
No operation		1 (0.7)	
Adjuvant therapy			
Received chemotherapy		50 (33)	
Received radiotherapy		118 (78)	
Received hormonal treatment		59 (40)	

Values in parentheses are percentage unless indicated otherwise. * values are mean (s.d.). Significant p-values are presented in bold. ^ Screening referral = women referred by the national breast cancer screening program.

In total 591 women were analysed, of whom 440 were diagnosed with BBD and 151 with BC. Women with BBD and BC were compared concerning demographic variables, personality at baseline and HCU (Table 1). In the BBD group the HCU for the GP, MD, and PS was significantly lower in the first year after diagnosis compared with the BC group (Table 2).
Subsequently, women were divided in four groups based on diagnosis (BBD or BC) and score on trait anxiety at baseline (HTA or NHTA). Women with BBD and HTA visited the GP more often than women with BBD and NHTA (p=0.003). The percentage of women with BBD visiting the MD was higher in women with HTA (p=0.043; Table 2). Concerning psychosocial care in the BBD group, women with HTA used this modality more frequently compared with women with NHTA (p<0.001). In women with BC and HTA more use of psychosocial care was found (p=0.002; Table 2).

Table 2 Health care utilization in the first year after diagnosis divided in four groups based on diagnosis, benign breast disease (BBD) and breast cancer (BC), and score on trait anxiety (high or not-high)

	Total group	High trait anxiety	Not-high trait anxiety	P
BBD	**N=440**	**N=72**	**N=368**	
GP visits				
Yes	306 (71)	53 (76)	253 (70)	0.358
Number *	2.3 (2.8)	3.2 (4.2)	2.1 (2.4)	**0.003**
MD visits				
Yes	227 (52)	45 (63)	182 (50)	**0.043**
Number *	1.6 (2.8)	1.9 (3.1)	1.5 (2.7)	0.249
PS use				
Yes	23 (5)	11 (15)	12 (3)	**<0.001**
BC	**N=151**	**N=42**	**N=109**	
GP visits				
Yes	118 (80)	31 (76)	87 (82)	0.377
Number *	3.1 (3.2) ^	3.7 (3.4)	2.9 (3.0)	0.157
MD visits				
Yes	127 (85)	37 (93)	90 (83)	0.130
Number *	6.9 6.6) °	7.2 (6.7)	6.7 (6.5)	0.711
PS use				
Yes	34 (23) >	16 (38)	18 (17)	**0.004**

Values in parentheses are percentage unless indicated otherwise. * values are mean (s.d.). Significant p-values are presented in bold, comparing groups with high or not-high score on trait anxiety. BC values significant higher compared to BBD: p-values ^ <0.001, ° 0.028, > <0.001. GP = general practitioner; MD = medical doctor; PS = psychosocial health care.

Multiple regression analyses for the BBD and BC groups revealed that the most important predictors for HCU in the BBD group were several domains of QoL, and in the BC group the type of operation and adjuvant treatment. Multiple regression analyses for the four groups based on diagnosis (BBD or BC) and trait anxiety (HTA or NHTA) revealed several predictors (Table 3).
In women in the BBD group with NHTA the predictors for increased HCU were lower scores on psychological, physical, general and environmental domains of QoL. In the BBD group women with HTA the predictors for increased HCU were not having work, lower score on general domain of QoL, and not having a partner (Table 3). In the BC group with NHTA the most important predictors for HCU were chemotherapy and lower score on social QoL, and in women with BC and HTA hormonal treatment, not having children, and educational level (Table 3).

Table 3 Outcomes of the multiple regression analyses on significant predictors for health care utilization (HCU) in the first year after benign breast disease (BBD) and breast cancer (BC) and the high (HTA) or not-high score on trait anxiety (NHTA)

HCU first year	Group	Independent factor	R^2	Beta	P
	BBD				
GP	NHTA	Environmental domain QoL Physical domain QoL	0.016 0.060	-0.152 -0.159	0.022 0.017
	HTA	Having work	0.111	-0.333	0.013
MD	NHTA	General domain QoL	0.051	-0.235	<0.001
	HTA	General domain QoL	0.086	-0.293	0.030
PS	NHTA	Psychological domain QoL	0.020	-0.140	0.011
	HTA	Having a partner	0.126	-0.355	0.007
	BC				
GP	NHTA	Social domain QoL Hormonal therapy	0.079 0.042	-0.285 0.205	0.005 0.042
MD	NHTA	Chemotherapy Type of operation	0.155 0.039	0.355 0.202	<0.001 0.034
	HTA	Having children Educational level Hormonal therapy	0.215 0.120 0.110	-0.619 0.345 0.336	<0.001 0.015 0.014
PS	NHTA	Having work	0.066	0.257	0.012

GP = general practitioner; QoL= quality of life; MD = medical doctor; PS = psychosocial health care. R^2 = percentage of variance in the scores of the dependent variable explained by the independent variable (1.00 = 100%); Beta: a negative Beta means that a higher score on the independent variable will result in a lower score of the dependent variable.

Discussion

The aim of the present study was to analyse the HCU and the possible predictors for HCU in women with BBD or BC during the first year following the diagnosis. An increase in HCU was expected in women with HTA irrespective of the diagnosis. Overall, women with BC were visiting the GP and the MD more frequently compared with women with BBD. In previous studies these findings are confirmed in women after BC treatment, even fifteen years after diagnosis the HCU is found to be higher.[12-14,27,28] This higher number of visits to the GP and MD is normal considering the BC (adjuvant) treatment during the first year. Subsequently, we found that chronically anxious women with BC used more psychosocial support during the first year after the diagnosis BC. This effect is not unexpected considering the higher levels of anxiety and lower QoL during the diagnostic process of suspected BC, especially in women with HTA.[7] In women with BC even five years after the diagnosis a higher use of mental health care is still found, especially because of anxiety and sleep disorders.[29] In women with BC no significant influence of HTA on GP and MD visits was seen. This effect is partly explained by the fact that all women with BC visit the GP and MD already very frequently as a part of their (adjuvant) treatment and follow-up protocol for BC. Apparently, even chronically anxious women experience this intensive standard follow-up as sufficient enough for comforting their fears and needs.

However, in women with BBD, HTA had an evident impact on the use of GP, MD and PS. Trait anxiety can be defined as a relatively stable individual difference in anxiety proneness.[11] Those chronically anxious women become even more anxious during the diagnostic process, and need more reassurance to confirm that the diagnosis is not BC. Apparently, this higher need for reassurance causes an increase in HCU. Previously, the higher need for reassurance was found especially in women with higher levels of anxiety and perceived stress.[8]

In addition, important predictors for increased HCU in the multivariate regression analysis were lower scores on several QoL domains at baseline, irrespective of diagnosis. QoL as predictor for HCU in women was not found before, but in previous studies QoL was measured with SF-36 or SF-12 and QOL-CS.[30,31] These questionnaires measure health status, which indicates whether there are limitations in physical possibilities, social activities, and state of mind, but reveals nothing about the feelings individuals have concerning their functioning. (General) QoL, however, also reflects to what extent a patient is bothered by limitations in daily life. Therefore, health status and QoL cannot be considered comparable or interchangeable for that matter.[32] It is known that trait anxiety has a very profound impact on QoL, this influence is even more important than the diagnosis being

BBD or BC.[4] The important influence of QoL on HCU is probably partly explained by this effect of trait anxiety on QoL. Apparently, chronically anxious women have an increased need for health care because the possibility of having BC is causing an extreme disturbance of their life with impaired QoL as a result.
To our knowledge, this is the first study analysing trait anxiety and QoL scores as factors for predicting HCU in women with BBD or BC. In this study a true and valid baseline measurement, i.e. before the diagnosis was known, of both trait anxiety and QoL was done. This study is based on self-reported use of health care. Therefore, an underestimation of HCU is possible because of the effort of recalling all medical contacts in the previous 12 months. However, in both groups (BBD and BC) the same method was applied. In addition, more women with BBD *and* HTA were found in the drop-out group. If these women had not dropped out, we can assume that our results would have been even more convincing.

Conclusions

The most important factors for increased HCU were HTA and lower scores on QoL, especially in women with BBD. In women with BC a higher PS use was seen in chronically anxious women. Therefore, it is very important to identify women with a lower QoL score and/or HTA with a psychometric test, who may need extra (psychosocial) health care during and after the diagnostic process in case of a first event of breast disease. These women can then be offered a tailor-made follow-up protocol which will anticipate to their specific (mental) health care needs after the diagnosis BBD or BC. Through this individual approach women who need more support will be recognized and this will prevent that these women are unnecessary suffering without receiving extra (psychosocial) health care.

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Chapter 6

Breast cancer or no cancer: the influence of diagnosis and personality on anxiety and depressive symptoms

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Submitted

Abstract

Background

High trait anxiety (HTA) determines high state anxiety and depressive symptoms in women with breast cancer (BC) and benign breast disease (BBD). We examined whether this is caused by the combination of personality *and* diagnosis or solely by the personality characteristic HTA.

Methods

Women with breast disease (BD, N=357), diagnosed with BC (N=152) or BBD (N=205) and gallstone disease (GD, N=128) were included in a prospective longitudinal study. Questionnaires concerning trait anxiety (baseline), state anxiety, and depressive symptoms were completed pre-diagnosis (BC and BBD) or before the laparoscopic cholecystectomy and six months later. Multivariate linear regression analysis was performed to analyse the predictors for state anxiety and depressive symptoms at six months.

Results

Pre-diagnosis women with BD scored higher on state anxiety ($p=0.001$) and depressive symptoms ($p<0.001$) compared with GD. At six months scores on depressive symptoms in BC remained higher than GD ($p=0.005$). Women with HTA scored unfavourably on state anxiety and depressive symptoms at all time points compared with women without HTA ($p<0.001$), especially women with BC. Regression analysis revealed that state anxiety and depressive symptoms at six months were predicted by depressive symptoms at baseline in women with BC.

Conclusions

The severity of diagnosis, i.e. BC, determines the impact on state anxiety and depressive symptoms in combination with HTA. Therefore, we recommend identifying those women with HTA or high state anxiety and/or depressive symptoms, and offer them a tailor-made follow-up protocol during and after the diagnostic process for BD.

Introduction

Breast cancer (BC) is the most common type of cancer among women. One in eight women in the western world will be diagnosed with BC.[1,2] However, the majority of women visiting a surgical outpatient clinic with breast problems are diagnosed with benign breast disease (BBD).[3] Up to 50 per cent of these women with BBD, like women with BC, experience high levels of anxiety and distress during the diagnostic process.[4-8] Before being diagnosed with BC, 28 per cent of women experience high levels of state anxiety in combination with depressive symptoms, which appears to be a major predictor of quality of life (QoL).[9] The adverse psychological effects are strengthened by personality, i.e. women with a high score on trait anxiety (HTA) report more state anxiety, depressive symptoms, or distress during and after the diagnostic process for BC or BBD.[5,6,8,10] Trait anxiety is defined as a relatively stable individual difference in anxiety proneness.[11] Thus, high state anxiety and depressive symptoms are important problems in women undergoing the diagnostic process for breast disease (BD = BC or BBD), especially in women with HTA. Therefore, we believe that a tailor-made follow-up protocol is required to prevent these adverse psychological consequences. However, before implementing such a protocol we need to know whether high state anxiety and depressive symptoms are caused by (the threat of) having BC or solely by the personality characteristic HTA. In other words, whether women with HTA experience high levels of state anxiety and depressive symptoms, irrespective of the diagnosis they are facing.

Therefore, in the present study we compared women confronted with a possible life threatening disease (i.e. BC) and women with a non-life threatening disease, i.e. gallstone disease undergoing a laparoscopic cholecystectomy (GD). We examined the predictive value of trait anxiety and diagnosis for state anxiety and depressive symptoms. The GD group was chosen because it was previously found that HTA has a negative impact on QoL and persisting biliary symptoms after the operation in this group.[12,13] We hypothesized that the severity of diagnosis, i.e. the suspicion of a malignant disease, will also be an important predictor for state anxiety and depressive symptoms, in addition to the personality characteristic trait anxiety.

In this prospective longitudinal study we assessed trait anxiety, state anxiety, and depressive symptoms in women with BD before diagnosis was known or before admission to the hospital for the laparoscopic cholecystectomy. State anxiety and depressive symptoms were assessed again six months later.

Patients and Methods

Participants

Women analysed for the present study were recruited for two different studies. In one study concerning the role of psychological factors on recovery after surgery, patients with GD awaiting an elective laparoscopic cholecystectomy in one teaching hospital in the Netherlands between March 2006 and January 2008 were asked to participate. Before admission for the cholecystectomy the first set of questionnaires was completed. Exclusion criteria were severe comorbidity (ASA III or more), complicated GD or liver disease, and previous upper abdominal surgery. In the other study concerning QoL in women with early stage BC or BBD, between September 2002 and June 2007 women who were referred to three teaching hospitals with an abnormality on a screening mammogram or with a palpable lump in the breast were invited to participate. Women with recurrent BD were excluded from this study. At baseline women completed the first set of questionnaires before any diagnostic procedures were carried out and, thus, before the diagnosis was known. For both studies women with an inability to read and write in Dutch, or (previous) psychiatric illness were excluded. The Medical Ethical Board of the primary research hospital gave approval of both study protocols. All participants gave written informed consent.

Questionnaires

Questionnaires were completed at baseline and at six months. The questionnaires assessed anxiety as personality characteristic at baseline (STAI-Trait), and experienced momentary anxiety (STAI-State) and depressive symptoms (CES-D) at baseline and at six months.

The Dutch version of the Spielberger State and Trait Anxiety Inventory (STAI) measures trait and state anxiety.[11,14] Trait anxiety concerns differences in individuals in the disposition to respond to stressful situations with varying amounts of stress. State anxiety is a momentary emotional condition characterized by subjective feeling of apprehension and tension. It is a widely used questionnaire with good reliability and validity.[11,14] High state anxiety was defined as a score greater than 38, and HTA with a score greater than 41.[14]

The Centre for Epidemiological Studies-Depression Scale (CES-D) was used to assess depressive symptoms. It measures both the presence and the degree of depressive symptoms. The psychometric properties are good.[15,16] In this study the 16-items version was used and a high score on depressive symptoms was defined as a score greater than 12.

At baseline, women were also asked to complete a questionnaire concerning demographic characteristics as age, paid work, marital status, and education level. The medical data concerning patient, diagnostic and treatment characteristics were obtained from the medical records.

Statistical procedures

Women who did not complete all questionnaires at six months were considered as drop-outs and excluded from further analysis. For examining differences between the drop-out and non-drop-out groups and between the three groups based on diagnosis (GD, BBD and BC) with regard to baseline characteristics, chi-square tests (discrete variables) and one-way ANOVA (continuous variables) were used. Differences in demographic characteristics at baseline were used as co-variables in the subsequent analyses. At baseline before diagnosis was known, BC or BBD, women were analysed as a whole group with BD.

A repeated measures general linear model (GLM) was used to examine scores on state anxiety and depressive symptoms across time (i) in the three groups GD, BBD and BC, and (ii) in patients with HTA or not-high score on trait anxiety (NHTA) in the GD, BBD and BC groups. When differences were found in the GLM between groups, one-way ANOVA was used to examine differences between groups at one particular measurement time. When differences were found in the GLM within one group concerning the scores at baseline compared with six months, paired t-tests were applied. Chi-square tests were used to analyse the changes of scores on state anxiety and depressive symptoms at six months compared with baseline (high or not-high).

The predictors for state anxiety and depressive symptoms (dependent variables) at six months were found using the diagnosis and demographic characteristics (block 1), scores on state anxiety and depressive symptoms at baseline (block 2), and trait anxiety (block 3) as independent variables in a multivariate linear regression analysis. A p-value < 0.05 was considered statistically significant. Statistical analyses were performed with SPSS® version 18 (SPSS, Chicago, Illinois, USA).

Results

During the study period in total 740 women were included. At six months 255 women did not complete all questionnaires and were excluded from further analysis. Women in the drop-out group were older ($p=0.040$) and were more often in the BD group compared with women who remained in the analysis ($p<0.001$). In total 485 women were included in the analysis: 128 women awaiting laparoscopic cholecystectomy for GD and 357 women with BD, of whom 205

women were diagnosed with BBD and 152 with BC. At baseline there were significant differences between groups concerning demographic characteristics, but no differences between groups were found concerning high scores on trait anxiety (Table 1).

Before diagnosis was known (BC or BBD) mean state anxiety scores at baseline were significantly higher in de BD group compared with GD ($p<0.001$; Table 1). At six months the state anxiety scores were significantly diminished in all three groups compared with the baseline scores ($p<0.001$), and no differences were found between groups. Concerning depressive symptoms women with BD scored higher at baseline compared with GD ($p<0.001$). At six months depressive symptom scores were decreased in all three groups ($p<0.001$), but scores in BC were significantly higher compared with GD ($p=0.005$; Table 1).

Table 1 Demographic, personality and psychological characteristics at baseline and at 6 months for four groups: gallstone disease (GD), benign breast disease (BBD), breast cancer (BC) and breast disease (BD, before diagnosis is known)

	GD N=128	**BBD N=205**	**BC N=152**		**P**
Demographics					
Age (years) *	46.2 (11.7)	53.8 (9.6)	57.2 (8.5)		‡, ~ <0.001 † 0.003
Partner	111 (87)	171 (86)	126 (84)		NS
Education > 14 yrs	35 (28)	40 (20)	25 (17)		‡ 0.004 ~ 0.016
Paid work	87 (69)	100 (49)	62 (41)		‡, ~ <0.001
Personality					
Trait anxiety score *	37.2 (9.6)	38.7 (11.0)	38.7 (11.1)		NS
High trait anxiety	33 (26)	62 (30)	52 (34)		NS
Psychological factors	**GD N=128**	**BBD N=205**	**BC N=152**	**BD N=357**	**P**
State anxiety baseline *	38.4 (10.5)	39.9 (13.2)	47.1 (14.0)	43.0 (14.0)	‡, † <0.001 ^ 0.001
State anxiety 6 months *	34.9 (12.0) °	34.3 (11.8) °	35.4 (11.7) °		NS
Depressive symptoms baseline *	7.5 (7.0)	10.9 (9.1)	10.1 (7.5)	10.6 (7.6)	‡ 0.024 ~, ^ <0.001
Depressive symptoms 6 months *	5.1 (7.0) °	7.0 (7.7) °	7.9 (7.5) °		‡ 0.005

Values in parentheses are percentages unless indicated otherwise; * values are mean (s.d.). ‡ = GD compared with BC, ~ = GD compared with BBD, † = BBD compared with BC, ^ = BD compared with GD. NS = not significant. ° = difference between baseline and six months is significant.

In the whole group a high score on anxiety at baseline was found in 164 women (34 per cent), of whom 61 women scored also high at six months (per diagnosis 24 in BC, 26 in BBD and 11 in GD). Concerning depressive symptoms at baseline a high score was found in 152 women (31 per cent), and at six months 65 women remained scoring high (per diagnosis 27 in BC, 31 in BBD and 7 in GD). Subsequently, women were divided in four groups (BD with HTA, BD with NHTA, GD with HTA, GD with NHTA) and in six groups when BD was split into BC and BBD based on diagnosis combined with the score on trait anxiety (HTA or NHTA). For each diagnosis group, women with HTA scored higher on state anxiety and depressive symptoms compared with women with NHTA at all time points ($p<0.001$; Table 2).

Table 2 Mean scores on state anxiety and depressive symptoms at baseline and at six months for the groups divided per diagnosis: gallstone disease (GD), breast disease (BD), benign breast disease (BBD) and breast cancer (BC), and score on trait anxiety (high or not-high)

	GD	**BD**	**BBD**	**BC**	**P**
High trait anxiety *	**N=33**	**N=114**	**N=62**	**N=52**	
State anxiety baseline	46.5 (10.4)	55.0 (11.7)	52.5 (12.4)	58.0 (10.2)	‡, ^ <0.001 ~ 0.040 † 0.030
State anxiety 6 months	46.2 (15.9)		44.9 (12.5) °	44.7 (10.3) °	NS
Depressive symptoms baseline	13.0 (7.8)	16.7 (8.8)	18.0 (9.6)	15.1 (7.7)	^ 0.030 ~ 0.020
Depressive symptoms 6 months	11.1 (9.7)		12.9 (9.8) °	13.4 (7.8)	NS
Not-high trait anxiety *	**N=95**	**N=243**	**N=143**	**N=100**	
State anxiety baseline	35.6 (9.1)	37.4 (11.1)	34.5 (9.2)	41.5 (12.3)	‡, † <0.001
State anxiety 6 months	31.0 (7.1) °		29.7 (8.0) °	30.6 (9.3) °	NS
Depressive symptoms baseline	5.6 (5.6)	7.7 (6.5)	7.9 (7.0)	7.5 (5.9)	^ 0.006 ~ 0.021
Depressive symptoms 6 months	3.0 (4.3) °		4.6 (5.0) °	5.0 (5.4) °	‡ 0.018

Values are mean (s.d.). ‡ = GD compared with BC, ~ = GD compared with BBD, † = BBD compared with BC, ^ = BD compared with GD. NS = not significant. ° = difference between baseline and six months is significant. * All values in women with high trait anxiety compared with not-high trait anxiety are significant different, $p < 0.001$.

High trait anxiety

At baseline *before* women were diagnosed with BC or BBD, scores on state anxiety ($p<0.001$) and depressive symptoms ($p=0.030$) were higher compared with GD (Table 2). At six months state anxiety was diminished in the BC and BBD group ($p<0.001$), without any change in the GD group, and no differences between the three groups were found. Concerning depressive symptoms, only in women

with BBD this score significantly diminished at six months (p=0.001; Table 2; Fig. 2). A high score at baseline and at six months on state anxiety per diagnosis was found in 20 women with BC, 24 in BBD and 11 in GD. Concerning depressive symptoms these numbers were 20 in BC, 26 in BBD and 5 in GD respectively (p=0.048).

Not-high trait anxiety

At baseline women in the BD group scored similar on state anxiety compared with GD (Table 2; Fig. 1). Concerning depressive symptoms, at baseline higher scores in the BD group were found compared with GD (p=0.006). At six months scores on state anxiety were decreased in all groups and no differences between groups were found. At six months the scores on depressive symptoms in all groups significantly diminished (p<0.001), and BC scored higher than GD (p=0.018).

Predictors of state anxiety and depressive symptoms at six months

The most important predictor for state anxiety at six months in the BC group was depressive symptoms at baseline (28 per cent of variance). For GD and BBD state anxiety at baseline was the most important predictor for state anxiety at six months (30 per cent and 26 per cent of the variance respectively). For depressive symptoms at six months in all three groups the most important predictor was depressive symptoms at baseline (Table 3). Trait anxiety was found to be predictive for state anxiety and depressive symptoms in addition to the baseline scores of these psychological factors themselves.

Table 3 Regression analyses for state anxiety and depressive symptoms at six months per diagnosis: gallstone disease (GD), benign breast disease (BBD) and breast cancer (BC)

Dependent factor	Diagnosis	Independent factor	R^2	Beta	P
State anxiety	**GD**	State anxiety Trait anxiety Education	0.296 0.106 0.049	0.386 0.364 -0.156	<0.001 <0.001 0.022
	BBD	State anxiety Trait anxiety	0.260 0.109	0.242 0.425	0.001 <0.001
	BC	Depressive symptoms Trait anxiety	0.265 0.089	0.235 0.371	0.010 <0.001
Depressive symptoms	**GD**	Depressive symptoms Trait anxiety Work	0.216 0.098 0.045	0.303 0.354 -0.197	<0.001 <0.001 0.008
	BBD	Depressive symptoms Trait anxiety	0.186 0.099	0.244 0.367	0.001 <0.001
	BC	Depressive symptoms Trait anxiety	0.275 0.105	0.341 0.372	<0.001 <0.001

R^2 = the proportion of variance in the scores of the dependent variable explained by the independent variable (1.00 = 100%); a negative Beta means that a higher score for the independent variable will result in a lower score for the dependent variable.

Figure 1 and 2 State anxiety (general mean scores) and depressive symptoms at baseline and at six months per diagnosis and per score on trait anxiety
NHTA = not-high trait anxiety, GD = gallstone disease, BBD = benign breast disease, BC = breast cancer, HTA = high trait anxiety

Fig. 1

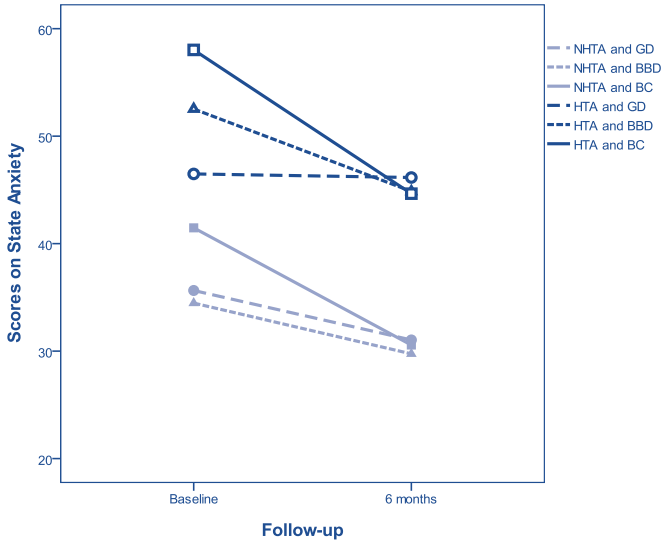
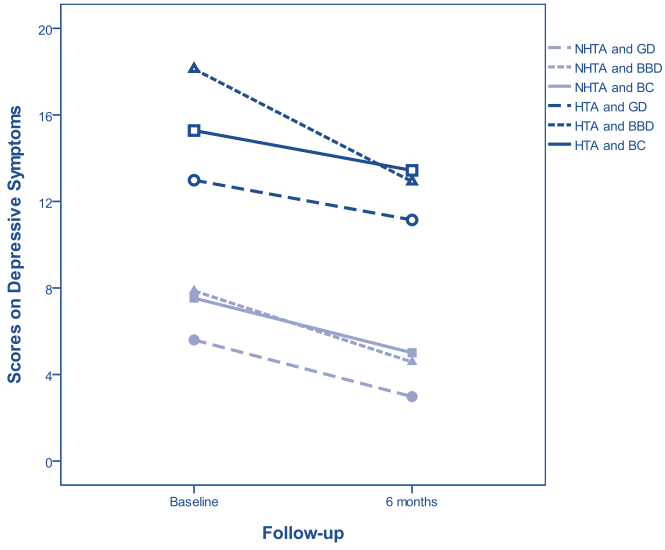


Fig. 2



Discussion

HTA determines high state anxiety and depressive symptoms in women with BC. We hypothesized that the possibility of having a life threatening disease, i.e. BC, will also be an important predictor for state anxiety and depressive symptoms, in addition to the personality characteristic trait anxiety.
As expected, the effects on state anxiety and depressive symptoms were heightened in women with HTA.[5,6,8,10] However, at baseline women in the HTA group with BD experienced more momentary anxiety than women with GD. Apparently in women with HTA the possible diagnosis BC is much more threatening than undergoing a laparoscopic cholecystectomy, which did not cause any changes in state anxiety in GD. Differences in state anxiety at baseline were also found in women in the NHTA group, women with BC experienced higher levels of state anxiety compared with GD or BBD. These findings confirm our previous study in which the fear of being diagnosed with BC, i.e. a false-positive screening mammogram, causes momentary anxiety not only in chronically anxious women but also in women who are not prone to anxiety.[17] Even though women with BD are all similarly referred to the outpatient surgical clinic with a palpable lump or after an abnormal screening mammogram, women diagnosed with BC were more anxious than women who appeared to have BBD, irrespective of HTA or NHTA. Apparently, these women eventually diagnosed with BC have an unconsciously awareness of possibly having BC, which explains the significant differences found between BBD and BC *prior* to diagnosis. These findings confirm our hypothesis that the threat of having BC has a serious impact on state anxiety, in addition to HTA.
Concerning depressive symptoms, women with BD scored higher compared with GD at baseline, which is found in women with HTA or NHTA. In contrast with state anxiety scores, depressive symptoms remained higher at six months in BC compared with GD in women with NHTA. In addition, in the HTA group more women with BC scored high on depressive symptoms at baseline *and* at six months compared with GD. Apparently, the threat of possibly having BC causes only severe momentary anxiety before diagnosis is known, but causes long-term effects such as depressive symptoms in women diagnosed with BC. Probably higher scores on depressive symptoms are not only caused by the BC diagnosis itself, but are also a result of the BC treatment.
The regression analysis revealed that state anxiety and depressive symptoms at six months is predicted by depressive symptoms at baseline in the BC group, up to 28 per cent of variance. In contrast, trait anxiety is also found to be a predictor but only up to a maximum of 11 per cent of variance. Thus, women diagnosed with BC

and a high score on depressive symptoms at baseline are at risk for ongoing anxiety and depressive symptoms six months after the surgery, which is strengthened in women with HTA.

Our present findings support our hypothesis that chronically anxious women do not always become more anxious and that the severity of diagnosis, i.e. benign or malignant breast disease versus GD, determines the impact on state anxiety and depressive symptoms in combination with HTA. These results are important to consider, because previously it was found that women with high scores on state anxiety *and* depressive symptoms prior to BC diagnosis, are at risk for impaired QoL up to two years after surgery.[9] In addition, both impaired QoL and HTA were found to be predictors for increased health care consumption up to one year after the diagnostic process in women with BBD.[18] In women diagnosed with BC *and* HTA increased use of psychosocial care was found one year after surgery.[18]

Conclusions

This study reveals that women who are confronted with the possibility of having BC, experience higher state anxiety and depressive symptoms prior to diagnosis than women with GD, these effects are heightened in women with HTA. Therefore, we recommend offering women with BD a psychometric test to identify those women with HTA *or* a high score on state anxiety and/or depressive symptoms prior to the diagnosis BC or BBD. These women should be offered a tailor-made support protocol during and after the diagnostic process for BD. With this individual approach, which will anticipate on specific (mental) health care needs, impaired QoL or increased health care utilization may be prevented.

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Chapter 7

Cancer or no cancer: the influence of personality and diagnosis on quality of life in breast cancer and benign disease

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Submitted

Abstract

Background

High trait anxiety (HTA) causes impairment in quality of life (QoL) and fatigue in women with breast cancer (BC) and benign breast disease (BBD). We examined whether the lowered QoL was caused solely by the personality characteristic HTA or the combination of personality and diagnosis.

Methods

Women with BC (N=152), BBD (N=205), and gallstone disease (GD, N=128) were included in a prospective, longitudinal study. Pre-diagnosis (BC and BBD) or before the laparoscopic cholecystectomy (GD) as well as six months later, questionnaires concerning trait anxiety (baseline), fatigue, and QoL were completed. Multivariate linear regression analysis was performed to analyse the predictors for QoL at six months.

Results

At six months QoL scores were significantly increased in the GD group, especially in women with not-HTA (NHTA), whereas fatigue remained stable across time, in both HTA and NHTA groups. At six months in women with NHTA and BBD the scores for fatigue and physical QoL had significantly improved, and in women with NHTA and BC a decrease in physical QoL and an increase in fatigue at six months were found. Women with HTA scored unfavourably on fatigue and QoL compared with women with NHTA at both time points. Regression analysis revealed that HTA and the change of fatigue score across time were the most important factors of influence concerning QoL.

Conclusions

The course of QoL and fatigue during follow-up were significantly different for each diagnosis. Particularly HTA had a negative impact on patients' QoL and fatigue. In addition, for some scales diagnosis also played a role. Especially the combination HTA *and* the diagnosis BC caused a negative impact on QoL and fatigue. We recommend identifying women with BC and HTA, who are at risk for diminished QoL, and offer them a tailor-made follow-up protocol.

Introduction

Breast cancer (BC) is the most common type of cancer among women. One in eight women in the western world will be diagnosed with BC.[1,2] Due to improvements in adjuvant treatment and early detection, BC is no longer a life threatening disease for many women.[3] As a result, long-term consequences of BC diagnosis and treatment, such as impairment in quality of life (QoL), are becoming more important. Diminished QoL has been found in women many years after BC treatment.[4,5] In contrast, a systematic review has found a good overall QoL in long-term BC survivors, but with BC specific problems.[6] Factors determining QoL are becoming a subject of great interest in order to prevent diminished QoL. QoL is predicted by factors such as adjuvant therapy, psychological distress, pain, arm morbidity, depressive symptoms, postmenopausal symptoms and fatigue.[7-9] Fatigue is a common problem during and after BC treatment, in up to 50 per cent of the women.[10-12] In addition, high trait anxiety (HTA) appears to influence QoL negatively[13-15], and determines the risk for developing fatigue in women with BC.[16] Trait anxiety is defined as a relatively stable individual difference in anxiety proneness, i.e. trait anxiety is a personality factor.[17]

Thus, impairment in QoL and fatigue are important problems in women with BC. In addition, fatigue itself is an important predictor for QoL.[7,8] Fatigue and QoL are both negatively influenced by the personality characteristic trait anxiety. Before implementing a tailor-made follow-up protocol for women with HTA to prevent adverse psychological problems after BC diagnosis and treatment, it is important to evaluate whether the diminished QoL is caused by (the threat of) having BC or solely by the personality characteristic HTA. In other words, whether women with HTA experience lowered QoL, irrespective of having a malignant or benign diagnosis.

To our knowledge, this is the first study comparing women with a possible life threatening disease (i.e. diagnosis BC and benign breast disease (BBD) known after baseline) and women with a non-life threatening disease, i.e. gallstone disease, undergoing a laparoscopic cholecystectomy (GD), with respect to QoL. The GD group was chosen because it was previously found that trait anxiety and fatigue have a negative impact on the QoL in this group.[18] We examined the predictive value of trait anxiety on the course of QoL and fatigue across time for the different diagnoses. We hypothesized that in addition to the personality characteristic trait anxiety the threat of a high impact disease (i.e. BC) will also be an important predictor of QoL. In addition, we analysed the impact of the change of fatigue across time on QoL, because fatigue is a serious problem in women with

BC[10-12] and is an important predictor for QoL.[7,8] In this prospective longitudinal study we assessed trait anxiety, fatigue, and QoL pre-diagnosis in women with breast disease or before admission to the hospital for the elective laparoscopic cholecystectomy. Fatigue and QoL were assessed again six months later.

Patients and Methods

Participants

Women analysed for the present study were recruited for two different studies. In one study concerning the role of psychological factors on recovery after surgery, patients were recruited in one teaching hospital in the Netherlands between March 2006 and January 2008. Patients with GD awaiting an elective laparoscopic cholecystectomy were asked to participate. The first set of questionnaires was completed before admission for the cholecystectomy. Exclusion criteria were severe comorbidity (ASA III or more), complicated GD or liver disease, and previous upper abdominal surgery. In the other study concerning QoL in women with early stage BC or BBD, women who were referred with an abnormality on a screening mammogram or with a palpable lump in the breast to three teaching hospitals were invited to participate between September 2002 and June 2007. Women with recurrent (benign) breast disease were excluded from this study. At baseline, before any diagnostic procedures were carried out and, thus, before the diagnosis was known, women completed the first set of questionnaires. For both studies, women with insufficient knowledge of the Dutch language or a (history of) psychiatric disease were excluded. The Medical Ethical Committee of the primary research hospital gave approval of both study protocols. All participants gave written informed consent.

Questionnaires

The questionnaires assessing trait anxiety (STAI-Trait), fatigue (FAS) and QoL (WHOQOL-Bref) were completed at baseline, i.e. before diagnosis was known in the breast disease group and before hospital admission in the GD group. The fatigue and QoL questionnaires were also completed at six months follow-up.
The Dutch version of the Spielberger State and Trait Anxiety Inventory (STAI) measures trait and state anxiety.[17,19] For this study only trait anxiety was used. It is a widely used questionnaire with good reliability and validity.[17,19] HTA was defined as a score greater than 41.[19]
Fatigue was measured by the 10-items Fatigue Assessment Scale (FAS).[20] The reliability and validity of the FAS appear to be good in women with breast problems and the general population.[20,21] The cut-off score was 22 or higher.

The World Health Organization Quality of Life assessment instrument-Bref is a generic, cross-culturally developed comprehensive measure of QoL.[22] It is the short version of the WHOQOL-100 questionnaire.[23,24] The WHOQOL-Bref measures QoL in four domains (Physical health, Psychological health, Social relationships and Environment) and the facet Overall QoL and general health. The psychometric properties of the WHOQOL-Bref are good, also in women with (benign) breast disease.[22,25]
At baseline, women were also asked to complete a questionnaire concerning demographic characteristics (age, paid work, marital status, and education level). The medical data concerning patient, diagnostic and treatment characteristics were obtained from the medical records.

Statistical procedures
Women who did not complete all questionnaires at six months were excluded from further analysis and considered as drop-outs. For examining differences between the drop-out and non-drop-out groups and between GD, BBD and BC, with regard to personality trait anxiety and demographic characteristics at baseline, chi-square tests (discrete variables) and one-way ANOVA (continuous variables) were used. Differences in demographic characteristics at baseline were used as co-variables in the subsequent analyses.
A repeated measures general linear model (GLM) was used to examine scores on fatigue and QoL across time (i) in the three groups GD, BBD and BC, and (ii) in patients with HTA or not-high score on trait anxiety (NHTA) in the GD, BBD and BC groups. When differences were found in the GLM between groups, one-way ANOVA was used to examine differences between groups at one particular measurement time. When differences were found in the GLM within one group concerning the scores at baseline compared with six months, paired t-tests were applied.
The predictors of QoL at six months after diagnosis (dependent variable) were found using the diagnosis and demographic characteristics (block 1), chemotherapy and/or radiotherapy in women with BC and the change of scores on fatigue across time (block 2), and trait anxiety (block 3) as independent variables in a multivariate linear regression analysis. A p-value < 0.05 was considered statistically significant. All analyses were performed with the Statistical Package for Social Sciences® (SPSS version 18.0).

Results

During the study period 740 women were included, of whom 255 women did not complete all questionnaires at six months and were excluded from further analysis. The demographic and personality characteristics at baseline were compared between drop-outs and non-drop-outs. In the drop-out group women were older ($p=0.040$) and breast disease was diagnosed more often ($p<0.001$). Concerning HTA no differences were found.

In total 485 women were included in the analysis, of whom 128 women with GD, 205 with BBD and 152 with BC. At baseline, significant differences between groups were observed concerning demographics. Women in the BC and BBD groups were older ($p<0.001$), had a lower level of education ($p=0.004$, $p=0.016$) and less women had paid work ($p<0.001$) compared with the GD group. Women with BC were older than women with BBD ($p<0.001$). High scores on trait anxiety were comparable between groups (Table 1). The percentage of women with HTA or high fatigue at baseline was not significantly different between groups.

In Table 2 mean QoL and fatigue scores are shown for the three patient groups at both time points. Subsequently, women were divided in six groups based on diagnosis (GD, BBD and BC) and the score on trait anxiety at baseline (HTA or NHTA). For each diagnosis women with HTA scored higher on fatigue and lower on QoL at both time points compared with women with NHTA ($p<0.001$; Fig. 1a-d, Fig. 2).

Table 1 Demographic and personality characteristics at baseline for three groups: gallstone disease (GD), benign breast disease (BBD) and breast cancer (BC)

	GD N=128	**BBD N=205**	**BC N=152**	**P**
Demographics				
Age (years) *	46.2 (11.7)	53.8 (9.6)	57.2 (8.5)	‡, ~, † <0.001
Partner	111 (87)	171 (86)	126 (84)	NS
Education > 14 yrs	35 (28)	40 (20)	25 (17)	‡ 0.004, ~ 0.016
Paid work	87 (69)	100 (49)	62 (41)	‡, ~ <0.001
Personality				
Trait anxiety score *	37.2 (9.6)	38.7 (11.0)	38.7 (11.1)	NS
Women with HTA	33 (26)	62 (30)	52 (34)	NS

Values in parentheses are percentages unless indicated otherwise; * values are mean (s.d.). NS = not significant. ‡ = GD versus BC, ~ = GD versus BBD, † = BBD versus BC, HTA = high score on trait anxiety.

Table 2 General and three domains of quality of life (QoL) and fatigue at baseline and at 6 months for three groups: gallstone disease (GD), benign breast disease (BBD) and breast cancer (BC)

	GD N=128		BBD N=205		BC N=152		P
QoL	**Baseline**	**6 months**	**Baseline**	**6 months**	**Baseline**	**6 months**	
General	7.0 (1.6)	7.7 (1.7)	7.5 (1.5)	7.7 (1.4)	7.6 (1.4)	7.6 (1.4)	‡ <0.001 ~ 0.003
Physical	13.7 (2.8)	15.7 (3.6) °	15.1 (2.6)	15.5 (2.7) °	15.5 (2.4)	14.9 (2.7) °	‡ <0.001 ~ <0.001
Psychological	14.3 (2.6)	15.1 (2.9)	14.5 (2.1)	14.6 (2.2)	14.9 (2.2)	14.7 (2.4)	
Social	15.9 (2.6)	15.4 (2.8)	15.9 (2.6)	15.7 (2.7)	16.6 (2.3)	15.9 (2.6)	‡ 0.030 † 0.013
Fatigue	21.0 (7.0)	21.2 (7.2)	21.3 (7.4)	20.0 (7.7) °	19.8 (7.3)	21.7 (7.7) °	

Values are mean (s.d.). ° = significant different between baseline and six months. Significant differences at baseline between diagnosis groups: ‡ = GD versus BC, ~ = GD versus BBD, † = BBD versus BC.

High trait anxiety

At six months in GD and BC the social QoL decreased (p=0.040 and p=0.001 respectively; Fig. 1d) compared with scores at baseline. In BBD, scores on QoL did not change across time. At baseline women with GD scored lower on all domains of QoL compared with BC, except for general QoL (Fig. 1a-d). Women with BBD scored higher on physical (p=0.036) and psychological QoL (p=0.001) than women with GD, and scores on social QoL were lower in BBD than in BC (p=0.001). At six months scores on psychological QoL were lower in the GD group compared with BBD (p=0.029) and BC (p=0.047). No differences or changes in the three diagnosis groups were found for fatigue scores at both time points (Fig. 2).

Not-high trait anxiety

During follow-up the scores in the GD group significantly increased for physical, psychological and general QoL (p<0.001; Fig. 1a-c). At six months the scores on physical QoL increased in the BBD group (p=0.011) and decreased in the BC group (p=0.004) compared with baseline. Women with GD scored lower on general and physical QoL at baseline compared with BC. At baseline women with BBD scored higher on physical and general QoL than GD, and no differences were found between BBD and BC. At six months scores on psychological QoL were lower in the BBD group compared with GD (p=0.001). At six months an increase in fatigue scores was found in BC (p<0.001) and a decrease in the BBD group (p=0.012), without changes in the GD group. At baseline a higher score on fatigue was found in the BBD group compared with BC (p=0.010), and at six months no differences between groups were found (Fig. 2).

Figures 1 and 2 Quality of life (QoL) and fatigue at baseline and at six months for each diagnosis and score on trait anxiety
NHTA = not-high trait anxiety, GD = gallstone disease, BBD = benign breast disease, BC = breast cancer, HTA = high trait anxiety

Fig. 1a

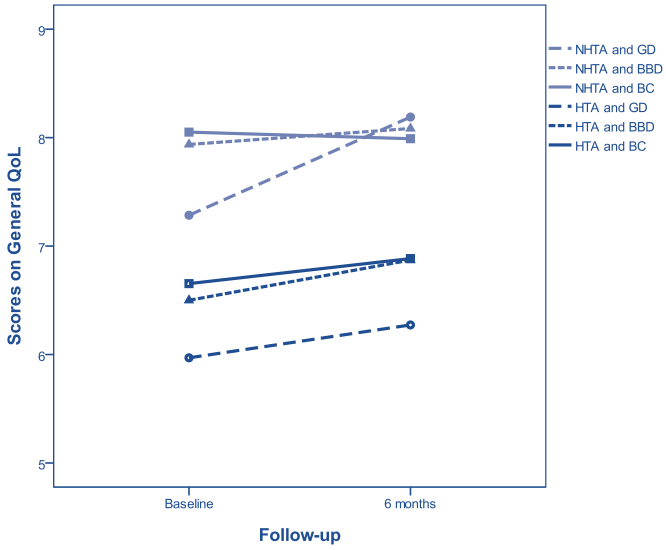


Fig. 1b

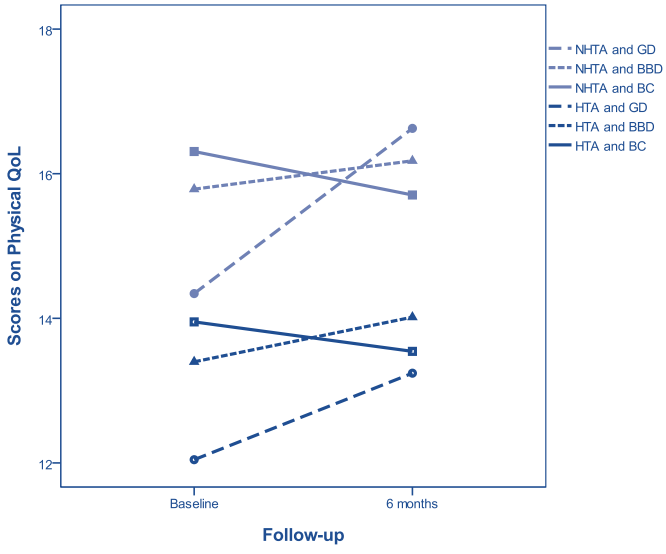


Fig. 1c

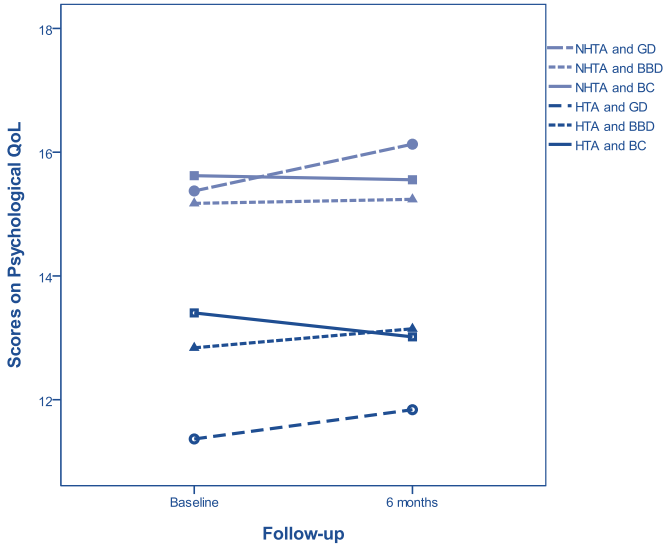

Scores on Psychological QoL
18
16
14
12
Baseline
6 months
Follow-up
NHTA and GD
NHTA and BBD
NHTA and BC
HTA and GD
HTA and BBD
HTA and BC

Fig. 1d

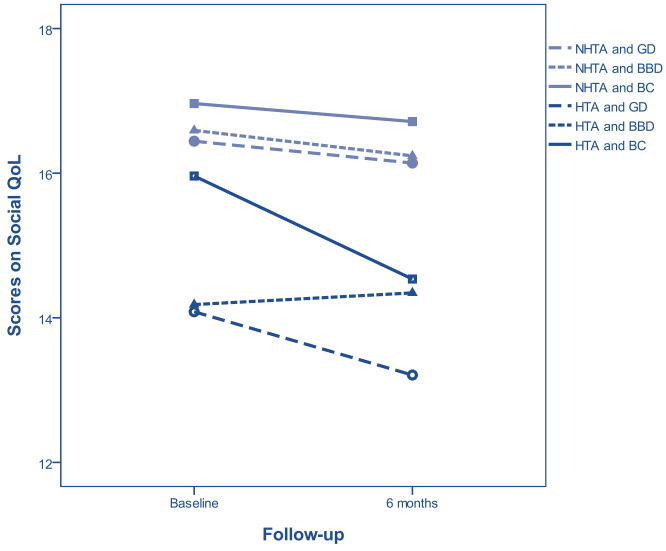
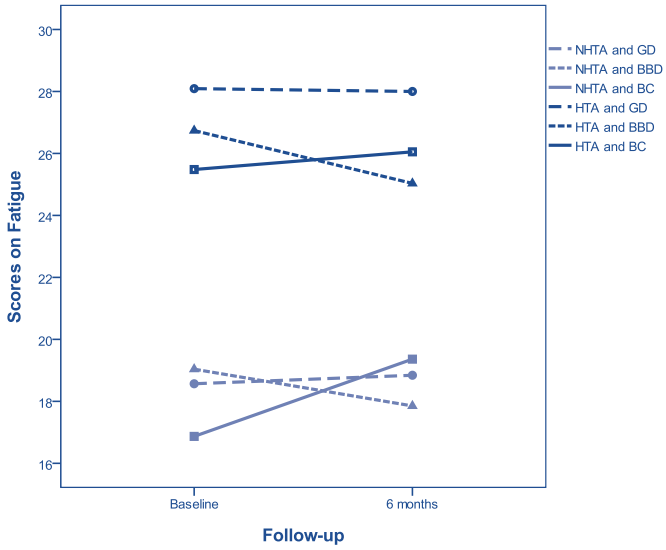

Scores on Social QoL
18
16
14
12
Baseline
6 months
Follow-up
NHTA and GD
NHTA and BBD
NHTA and BC
HTA and GD
HTA and BBD
HTA and BC

Fig. 2



Predictors of quality of life at six months

Regression analysis for the whole group and per diagnosis revealed that HTA and the change of scores on fatigue across time were the most important factors of influence concerning QoL at six months (Table 3). HTA was found to be the most important predictor for QoL in all three groups, up to 20 per cent in BBD and 28 per cent in BC, and 44 per cent in the GD group. Up to 10 per cent of variance in the scores in the BC group was explained by change of scores on fatigue across time, in the GD and BBD groups, for 7 per cent and 13 per cent respectively.

Table 3 Regression analyses for general and three domains of quality of life (QoL) at six months for each diagnosis

	Dependent factor	Independent factor	R^2	Beta	P
GD	General QoL	Fatigue change Trait anxiety Partner	0.065 0.255 0.047	-0.274 -0.509 0.145	<0.001 <0.001 0.049
	Physical QoL	Work Trait anxiety	0.080 0.159	0.253 -0.400	0.002 <0.001
	Psychological QoL	Fatigue change Trait anxiety	0.038 0.439	-0.213 -0.663	0.001 <0.001
	Social QoL	Trait anxiety	0.217	-0.466	<0.001
BBD	General QoL	Fatigue change Trait anxiety	0.084 0.150	-0.316 -0.397	<0.001 <0.001
	Physical QoL	Fatigue change Trait anxiety	0.126 0.133	-0.366 -0.365	<0.001 <0.001
	Psychological QoL	Fatigue change Trait anxiety	0.117 0.203	-0.359 -0.451	<0.001 <0.001
	Social QoL	Trait anxiety Fatigue change	0.111 0.061	-0.333 -0.261	<0.001 <0.001
BC	General QoL	Fatigue change Trait anxiety	0.049 0.178	-0.269 -0.425	<0.001 <0.001
	Physical QoL	Fatigue change Trait anxiety	0.102 0.192	-0.373 -0.442	<0.001 <0.001
	Psychological QoL	Fatigue change Trait anxiety	0.064 0.275	-0.321 -0.529	<0.001 <0.001
	Social QoL	Trait anxiety	0.168	-0.410	<0.001

GD = gallstone disease, BBD = benign breast disease, BC = breast cancer. R^2 = percentage of variance in the scores of the dependent variable explained by the independent variable (1.00 = 100%); Beta: a negative Beta means that a higher score on the independent variable will result in a lower score of the dependent variable.

Discussion

HTA causes impairment in QoL in women with BC and BBD.[13-15] However, whether these effects are caused by (the threat of) having BC or solely by the personality characteristic HTA has not been examined before. Therefore, the aim of this prospective longitudinal study was to analyse the impact of diagnosis, i.e. malignant or benign disease, on QoL. We hypothesized that in addition to the personality characteristic trait anxiety the threat of a high impact disease (i.e. BC) is also an important predictor of QoL.

At baseline women with GD scored lower on several domains of QoL compared with BC, regardless of HTA. These lower scores can be explained by the daily

and/or long term complaints caused by the GD in contrast with women with (benign) breast disease without such restrictive physical problems. This is reflected by the fact that several scores on QoL significantly increased at six months in the GD group due to the relief of symptoms after the operation. This improvement of QoL was mainly found in women with NHTA. Perhaps it takes more than six months to overcome the impact of undergoing a laparoscopic cholecystectomy in women with HTA.

In women with NHTA and BBD, the relief that BC was not found could explain why the scores for fatigue and physical QoL were significantly improved at six months. Only in women with NHTA these changes were found, probably it takes more than six months for women with HTA to overcome the threat of possibly having BC. In women with NHTA and BC the decrease in physical QoL and increase in fatigue at six months are not unexpected because of the possible side-effects of BC treatment. Thus, the change in QoL and fatigue during six months is significantly different for each diagnosis, in particular in women with NHTA. The changes can be explained by symptoms caused by either the disease or the medical treatment thereof.

Women with HTA scored unfavourably on fatigue and QoL compared with women with NHTA at both time points, which is in accordance with previous studies.[13-16] Trait anxiety was found to be the most important factor of influence on QoL, in particular in women with GD up to 44 per cent, whereas in women with BC or BBD 28 and 20 per cent respectively. Thus, in women confronted with a possible life threatening disease, i.e. BC or BBD, the impact of HTA is less important than in women with a non-life threatening disease, i.e. GD. Apparently, the diagnosis BC is much more threatening than GD, regardless of HTA. Thus, women with GD *and* HTA have a high risk for impairment in QoL, which is confirmed by the lower scores on psychological QoL at six months compared with BBD or BC.

The other factor of influence on QoL at six months was the change of fatigue scores across time in all three diagnosis groups, within the BC group up to 10 per cent of variance. Only in women with BC we found that fatigue was significantly increased at six months compared with baseline. This implies that the diagnosis BC and probably even more its treatment determines, as a result of fatigue, the impact on QoL. The effects of BC diagnosis and its treatment could explain this ongoing fatigue.[4,9-12] Our findings are in accordance with previous studies in which fatigue had the greatest impact on QoL in women with BC.[7,8] Thus, these results strengthened our hypothesis that the severity of the diagnosis, i.e. benign or malignant disease, and the (medical) consequences of the diagnosis are predictors for QoL, in addition to the most important factor of influence the personality characteristic trait anxiety.

Conclusions

The present study reveals that the pattern and changes in QoL during follow-up were significantly different for each diagnosis. Especially HTA had a negative impact on patients' QoL and fatigue. In addition, for some scales diagnosis also played a role. Particularly the combination HTA *and* the diagnosis BC caused a negative impact on QoL and fatigue. Therefore, we recommend identifying women with HTA who are at risk for adverse psychological effects with a psychometrically sound test. Those women with BC *and* HTA can then be offered a tailor-made support protocol. With this individual approach, which will anticipate on specific (mental) health care needs, impairment in QoL may be prevented.

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Chapter 8

Summary, discussion, clinical implications and future perspectives

Summary

Breast cancer screening program and its psychological consequences

In the 1960s the breast cancer (BC) screening program has been introduced to achieve earlier detection with the potential to reduce BC mortality. However, recent studies suggested that screening has little detectable impact on BC mortality.[1-3] The disadvantages of the BC screening program, such as overdiagnosis, overtreatment, and a false-positive screening mammogram (FP) may have substantial consequences for women attending the BC screening program.[3,4] As a consequence, recent publications have been discussing the screening controversy by questioning whether the benefits still justify the harms of the BC screening program.[1-10]

To contribute to this ongoing discussion, the aim of the first part of this thesis was to determine the impact of an abnormal screening mammogram (ASM) on women's psychological distress (state anxiety, depressive symptoms) and quality of life (QoL). Only a few studies have examined the impact of an ASM on health status or health-related QoL. Health status or health-related QoL measure the impact of disease on functioning, whereas QoL also reflects to what extent a patient is bothered by these limitations in daily life.[11] Therefore, we measured QoL with the WHOQOL questionnaire which asks about satisfaction and not merely functioning. Previous reviews have described serious psychological consequences after an FP.[12-15] However, examining the impact of the personality characteristic trait anxiety on the psychological consequences after an FP has not been done before. Trait anxiety refers to relatively stable individual differences in anxiety proneness.[16] Also, comparing women with regard to the timing of the ASM (first versus repeat), or comparing women with benign breast disease (BBD) referred after an ASM or referred with a palpable lump was not performed before.

Chapter two describes the impact of an FP on state anxiety and QoL until one year after diagnosis. In addition, the diagnostic process after an ASM was investigated. Women with an FP (N=233) were compared with women diagnosed with BC (N=152) after an ASM. Prior to diagnosis, women with BC were more anxious than women with an FP and experienced a decline in QoL one month after surgery. In the group with a high score on trait anxiety (HTA), women with an FP scored as high on state anxiety as women diagnosed with BC. Women with an FP and HTA reported diminished QoL until one year after the diagnosis compared with women with FP and without HTA (NHTA). These scores were even lower compared with women diagnosed with BC and HTA. Significantly more diagnostic

procedures (including biopsies) were needed in the FP group to reach the final benign diagnosis. Only 28 per cent of the women in the FP group could be diagnosed as BBD with a repeat mammogram. During the first year after screening, 55 per cent of the FP group returned to the outpatient clinic, some women up to eight times. Thus, women with HTA experienced high levels of momentary anxiety and impairment in QoL, regardless of being diagnosed as an FP or with BC. Being recalled for further diagnostic investigations after an ASM resulted in more histological biopsies and a high number of revisits to the outpatient clinic in the FP group.

In **chapter three** we were especially interested in the timing of an ASM, i.e. first (N=186) or repeat (N=296) screening mammogram. We examined the effect of timing on psychological distress (state anxiety, depressive symptoms) and QoL. We hypothesized that being referred after a first ASM evokes more distress and impaired QoL compared with women referred after a repeat ASM. Those women with a repeat ASM have attended the program before without any problems and are, thus, “more experienced”. Therefore, we compared women referred for further additional investigation after a first ASM or after a repeat ASM. All women experienced high levels of anxiety and depressive symptoms before diagnosis was known compared with one month after the diagnosis. Prior to diagnosis, in the group of women with NHTA, higher state anxiety levels were found in the first ASM group than in the repeat ASM group. HTA was predictive for more state anxiety, depressive symptoms, and impaired QoL. Thus, negative psychological consequences after an FP are seen in all women. These effects are more heightened in women with HTA. Attending the screening program for the first time evoked more anxiety in women with NHTA.

In **chapter four** we examined whether the previously found adverse psychological effects are found in all women diagnosed with BBD or in particular after an ASM. Women attending the BC screening program usually have no symptoms and, as a consequence, are not expecting an ASM. We hypothesized that these women are more alarmed by being recalled for further diagnostic procedures than women referred with a palpable lump in the breast. Women diagnosed with BBD after an ASM (N=363) were compared with women with a benign palpable lump in the breast (N=401). A similar score on state anxiety was found in both groups. A lower psychological QoL score at 12 months was seen in the ASM group. In women with NHTA, those in the ASM group were more anxious with more depressive symptoms prior to diagnosis compared with the women with a palpable lump in the breast. Within the NHTA group, women with an ASM reported lower psychological

QoL at baseline and at 12 months than women with a palpable lump. Women with HTA scored unfavourably on anxiety, depressive symptoms and QoL compared with women with NHTA. Thus, ASM evoked more anxiety and depressive symptoms prior to diagnosis with an ongoing impairment of QoL compared with women referred with a benign palpable lump in the breast, especially in women not prone to anxiety.

High trait anxiety and (benign) breast disease

Trait anxiety concerns differences in individuals in the disposition to respond to stressful situations, such as a possible diagnosis of BC, with varying amounts of stress.[16] Previous studies have revealed a negative impact of the personality characteristic trait anxiety on state anxiety, depressive symptoms, and QoL in women with BC and/or BBD.[17-21] We believe that a tailor-made follow-up protocol would be useful to prevent adverse psychological consequences in women with HTA during and after the diagnostic process for possibly having BC.

Therefore, the second part of this thesis focuses on the impact of the personality characteristic trait anxiety on health care utilization, psychological distress (state anxiety, depressive symptoms), and QoL in women with benign or malignant (breast) disease. To our knowledge, examining the impact of HTA on health care utilization has not been done before in women diagnosed with BC or BBD. Furthermore, we hypothesized that the severity of diagnosis, i.e. being confronted with a possible malignant breast disease, will also be an important predictor for psychological distress, in addition to the personality characteristic trait anxiety. In order to study this hypothesis, we compared women suspected of having BC or BBD with women with gallstone disease awaiting an elective laparoscopic cholecystectomy. The group of women with gallstone disease was chosen, because it was previously found that HTA had a negative impact on QoL and persisting symptoms in this group.[22,23]

Such a comparative study to assess the influence of the personality and the combination of personality *and* diagnosis on QoL and psychological distress has not been done before. Before implementing a protocol for women with breast disease *and* HTA, it is important to know whether women with HTA experience higher levels of distress and impairment of QoL, irrespective of the diagnosis they are facing or in particular when suspected of having BC.

In **chapter five** we evaluated the health care utilization and its predictors in women diagnosed with BC or BBD. Health care utilization was measured during the first year following the diagnostic work-up for breast disease. Health care utilization was divided in visits to the general practitioner, the medical doctor or psychosocial

care. Women diagnosed with BC (N=151) were compared with women with BBD (N=440). Overall, women with BC were visiting the general practitioner, the medical doctor or psychosocial care more frequently than women with BBD. This higher health care utilization in women with BC is a consequence of the BC (adjuvant) treatment and follow-up protocol. In the BBD group, in women with HTA increased overall health care utilization was found compared with women with NHTA. In women with BC and HTA only more use of psychosocial care was found. Regression analysis showed that lower scores on QoL predicted health care utilization in BBD. In women with BC (adjuvant) treatment predicted health care utilization. Thus, the most important factors for increased health care utilization were HTA and lower scores on QoL, in particular in women with BBD. In women with BC a higher use of psychosocial care was found in chronically anxious women.

In **chapter six** we analysed whether high state anxiety and depressive symptoms in women with BC or BBD are determined solely by the personality characteristic trait anxiety, or whether it is caused by personality in combination with the severity of diagnosis, a possible life-threatening disease (i.e. BC). To examine this, we compared women with breast disease with women with a non life-threatening disease, i.e. gallstone disease. Women with breast disease were included before diagnosis was known (BC or BBD), and women with gallstone disease before the elective laparoscopic cholecystectomy. Prior to diagnosis women with BC or BBD (N=357) were more anxious compared with gallstone disease (N=128). Scores on depressive symptoms at baseline were higher in women with BC or BBD compared with gallstone disease. At six months scores on depressive symptoms remained higher in BC (N=152) compared with women with gallstone disease. Women with HTA scored unfavourably on state anxiety and depressive symptoms at all time points compared with women with NHTA, especially women with BC. Thus, women who were confronted with the possibility of having BC, experienced higher state anxiety and depressive symptoms than women with gallstone disease. These effects were heightened in women with HTA. It is the combination of the diagnosis BC and HTA that evoked the highest levels of distress.

In **chapter seven** the impact of trait anxiety and/or the severity of diagnosis on QoL was examined. We compared women with BC or BBD with women with gallstone disease. Women with HTA scored unfavourably on fatigue and QoL compared with women with NHTA at baseline and at six months. At referral women with gallstone disease scored lower on several domains of QoL compared with BC, regardless of the score on trait anxiety. At six months these scores significantly

increased in the gallstone disease group with NHTA, probably due to the relief of symptoms after the operation. In women diagnosed with BBD and NHTA the scores on fatigue and physical QoL improved at six months, which can be explained by the relief that BC was not found. Women diagnosed with BC and NHTA experienced impairment in physical QoL and fatigue six months after the surgery. These findings were not unexpected because of the effects of BC diagnosis and its treatment. The most important factors of influence on QoL were HTA and the change in scores on fatigue across time. Thus, the course of QoL and fatigue during follow-up was significantly different for each diagnosis. Especially, HTA had a negative impact on patients' QoL and fatigue. In particular, the combination HTA and the diagnosis BC caused a negative impact on QoL and fatigue.

Discussion

Nowadays, BC screening has become standard of practice in the Western World. The BC screening program was implemented to obtain earlier detection of BC with the potential to reduce BC mortality. In the Netherlands, several studies have demonstrated that BC screening contributes to the decline of BC mortality.[24-26] In other countries with long-standing BC screening programs, the beneficial effect of screening on BC mortality was also confirmed.[27] However, if reduction in BC mortality is due to screening, one would expect that there is a decrease in diagnosing advanced BC. This is not the case during the 12 years of biennial screening in the Netherlands.[28] Moreover, it is suggested that BC screening has only a little detectable impact on BC mortality.[1-3] This conflicting evidence is partly explained because of the fact that the reduction of BC mortality was found in suboptimal performed trials, and that the trials with adequate randomisation did not reveal any impact on BC mortality.[3] Several studies suggested that the decline in BC mortality is accomplished only by the improvements of adjuvant BC treatment.[29-31] As a consequence, recent publications have been questioning whether the benefits still outweigh the harms of the BC screening program.[1-10] To contribute to this ongoing discussion, we examined the impact of an ASM on women's psychological distress and QoL.

The first part of this thesis reveals that the impact of an ASM on state anxiety, depressive symptoms and QoL is substantial and causes a serious problem. Not only chronically anxious women experienced the diagnostic process for breast disease as a great emotional burden. Also women not prone to anxiety reported significant adverse psychological consequences during and after the diagnostic work-up for an ASM. In 79 per cent of the women with HTA abnormal levels of

anxiety were found prior to diagnosis, as well as in up to 30 per cent of the women with NHTA. The fact that women with NHTA are also severely affected implies that being recalled for further diagnostic procedures after an ASM is a serious psychological problem. These women do not have a high propensity to anxiety, thus, the abnormal levels of anxiety are directly caused by the threat of possibly having BC. In our opinion, these findings are unacceptable, because we have found not only short-term effects, but also long-term consequences. Even though the distress was decreased one month after diagnosis, a diminished QoL was still found one year later, regardless of the score on trait anxiety. This implies that the psychological distress is not just a temporary problem. Moreover, women with an FP and HTA reported even more impairment in QoL after one year than women with BC and HTA. This ongoing impairment in QoL can be considered as a long-term consequence of the experienced distress during the diagnostic work-up after an ASM. The long-term effects after an ASM are confirmed by the fact that 55 per cent of the women frequently visited the outpatient surgical clinic in the first year after the FP. Apparently, these women needed more reassurance to confirm that their diagnosis was not BC. This higher need for reassurance is not unexpected, as being recalled *without* any symptom is very alarming. These women did not have a palpable lump in the breast or any complaints and so were not expecting an ASM followed by further additional (invasive) investigations. This might explain the increased visits during the first year after diagnosis. These findings confirm the severe impact of an ASM on the psychological health of women attending the BC screening program. The results of this thesis are in concordance with previous reviews describing the adverse psychological consequences after an FP.[12-15] In contrast to the majority of the included studies in these reviews, in our study the questionnaires were completed *before* the diagnosis BC or BBD was known. This renders a true baseline measurement and makes our findings even more convincing.

The second part of this thesis examined whether women with HTA are always experiencing increased distress and impairment in QoL, or whether the diagnosis itself, i.e. BC, is also an important predictive factor. Our findings are in accordance with previous studies, revealing a negative impact of HTA on distress and QoL in women with BC or BBD.[17-21] Moreover, we found that in women with HTA the possible diagnosis BC is much more threatening than undergoing surgery for gallstone disease. Before diagnosis is known, in the group of women with HTA, women with BC were more anxious than women with BBD, and women with BBD were more anxious than women with gallstone disease. Thus, it is the combination of the diagnosis BC and HTA, which causes the highest levels of anxiety. In

addition, HTA had a significant impact on health care utilization in women diagnosed with BBD one year after the diagnostic work-up. Furthermore, in women confronted with the possibility of having BC, the impact of HTA on QoL was less important than in women with gallstone disease. In women with BC other factors were also important for determining QoL, such as increased fatigue. It is the severe impact of the possible diagnosis BC that determines directly the increased distress, impairment in QoL and health care utilization, and these findings are heightened in women with HTA. Therefore, these results confirm that the negative impact of an ASM on distress and QoL in women with HTA is caused by the combination of being suspected of having BC *and* HTA, instead of only by the HTA.

This thesis shows that being diagnosed with an ASM evokes serious distress and impairment in QoL, regardless of the score on trait anxiety. In the Netherlands, the risk for an FP is 9 per cent when attending 13 screening rounds.[32] This relatively low number is explained by the much lower recall and FP rate in the Netherlands compared with other countries.[32] For instance, the risk for an FP is estimated to be 49 per cent after ten mammograms in the United States and up to 21 per cent in Norway.[33,34] Because of this higher chance of an FP, the adverse psychological consequences found in this thesis are expected to be an even more serious problem in the United States. Since BC screening is offered to healthy women, we believe that the disadvantages should be kept to a minimum. Obviously, every screening program has certain harms, but the benefits should significantly outweigh these harms. However, in this thesis we found adverse psychological problems in *all* women referred after an ASM. As it concerns healthy women without symptoms or signs of breast disease, we consider these effects as severe and undesirable consequences of BC screening. Especially, considering the minor effect on BC mortality previously found[1-3], we believe that the negative consequences after an ASM found in this thesis are really unnecessary and thus unacceptable. Therefore, in our opinion the balance between the advantages and disadvantages of the BC screening program can no longer be considered in favour of screening. Based on previous findings and this thesis we agree with several authors who already made a plea to re-evaluate the rationale of the BC screening program![5,10,30]

Methodological limitations of the study

The study has a number of methodological limitations. The first shortcoming is that we included women referred after an ASM to investigate the impact of the BC

screening program. However, in the Netherlands, the recall rate is approximately 2 per cent.[35] Thus, we have no information on the amount of distress in women who are diagnosed with a normal screening mammogram. Preferably, all women should complete the questionnaires before the screening mammogram is done. This would be an even better baseline measurement than we have done in this present study, i.e. after referral, but before diagnosis was known.

One of the other limitations of the study is the participation rate. Overall, the participation rate was approximately 65 per cent. Reasons for not participating in the study were the length of the questionnaires, the amount of stress prior to diagnosis and as a consequence, the feeling not being able to complete the questionnaires. Therefore, our results may well be an underestimation of the experienced distress and impairment of QoL, because it appears that more distressed women did not participate in our study.

Another drawback is the drop-out rate of the study, which was approximately 35 per cent. Women who did not complete all questionnaires during follow-up were excluded from further analysis. Baseline demographics and personality were compared between drop-outs and women who remained in the study. In particular, in the drop-out group more women were diagnosed with BBD or with HTA. As a consequence, we can assume that our results would have been even more convincing if those women with HTA had completed all questionnaires during follow-up.

HCU was measured with self-reported use of health care during the first year after the diagnosis BBD or BC. Therefore, an underestimation of health care utilization is possible because of the effort of recalling all medical contacts in the previous 12 months. Thus, our results would probably have been more convincing if the health care utilization was prospectively followed and objectively measured. However, in both groups, BC and BBD, the same method was applied.

Overall, the follow-up period in our study was up to 12 months. We believe that a longer follow-up period is important to investigate how long the impact of an ASM persists.

Clinical implications

This thesis shows that the impact of the BC screening program on distress and QoL is a serious problem after an ASM, both in women with HTA or NHTA. Based on these findings we advocate that as long as screening continues two important topics should be improved. Firstly, the decision to participate to the BC screening program is based upon information in favour of screening without mentioning the serious disadvantages.[3,6-8,36,37] As a result women overestimate their risk of BC

and the benefits of screening and are not aware of the possible dangers.[38,39] We recommend that women are informed correctly concerning the benefits ánd risks of the BC screening program, in particular mentioning the risk for overdiagnosis and the substantial psychological consequences after an FP. With this balanced information women will be able to choose whether or not to accept the invitation to the BC screening program.

Secondly, we recommend identifying women who are at risk for the adverse psychological effects, in particular women with HTA, with a psychometrically sound self-report questionnaire at intake. These women can then be offered a tailor-made follow-up protocol, which should be developed for women with HTA. Through this individual approach, women who need more support can be recognised and can be offered psychosocial interventions that focus on learning how to cope with these stressful events.

Future perspectives

Based on the findings of this thesis it is important to improve the information provided to women attending the BC screening program. Future research will be necessary to investigate the impact of providing evidence based information on the attendance rate and the experienced distress and QoL. Furthermore, a longer follow-up period than one year will be required to measure how long the negative impact of an ASM persists. Also, the effect of an ASM on the re-attendance rate and the health care utilization should be examined.

In addition, women at risk for the adverse psychological consequences after an ASM should be offered a tailor–made follow-up protocol when necessary. It is important to examine the impact of this protocol on distress, QoL and health care utilization during and after the diagnostic work-up for breast disease. In this way we will be able to investigate the implementation and if necessary can adjust this protocol.
Also, women should be identified who will benefit from this tailor-made follow-up protocol. Women with HTA can be assessed with the short version of the STAI-Trait questionnaire.[16] However, also women with NHTA are at risk for serious psychological effects after an FP. These women should be offered a validated self-report questionnaire to screen women at risk for adverse psychological problems diagnosed with BBD. Recently, the Psychosocial Distress Questionnaire-Breast Cancer was developed for women with early-stage BC.[40,41] It was found that this is an easy and useful instrument to screen psychosocial problems in women with

BC.[40,41] For women diagnosed with BBD after an ASM, this questionnaire should be tested and validated before it can be used in this group of women.

To contribute to the ongoing discussion concerning the BC screening program future research should focus on several important topics.
Firstly, in this study, women were included who were referred after an ASM for further additional investigations. The recall rate in the Netherlands is only 2 per cent.[35] This implies that we have no information about the experienced distress and QoL in women who are not referred (98 per cent). We are interested in the short- and long-term experienced distress and QoL in those women with a normal screening mammogram. We suggest to investigate (the impact of HTA on) distress, health care utilization and concerns about possibly having BC before and after attending the BC screening program in this particular group of women. Thus, *all* women should be asked to complete the questionnaires *before* undergoing the screening mammogram. When the results of the screening mammogram are known, *all* women should fill in the questionnaires again, to determine the psychological effects of being referred or reassured after a screening mammogram.

Secondly, we are interested in women recalled after an ASM, who undergo further additional investigations, such as a repeat mammogram, eventually followed by biopsies or a MRI. In our experience, undergoing a MRI often leads to an extra ultrasound investigation of the breast, which is frequently completed by a biopsy. In clinical practice, some women are then recalled again after 6 months for a repeat mammogram or MRI to achieve even more reassurance about the diagnosis BBD. In the Netherlands, only in 70 per cent of the women the diagnosis is known within three months after the ASM.[35] We expect that the longer the period of additional (invasive) investigations is, and thus the longer women have to wait for the final diagnosis, the more distress these women will experience. We believe it is necessary to examine the impact of the further (invasive) investigations on distress, QoL and health care utilization in women recalled after an ASM, and to offer these women extra psychosocial support when necessary. In addition, the diagnostic process has to be evaluated to examine the possible delay during this process, and the unnecessary or ineffective investigations. With this information it will be feasible to improve the diagnostic process in women after an ASM.

Thirdly, we believe it is important to determine the adverse psychological consequences in women with screen-detected ductal carcinoma in situ (DCIS). Overdiagnosis is an important problem of BC screening, which means detecting

lesions that would otherwise never have been identified clinically. Overdiagnosis due to BC screening was found in a meta-analysis in up to 52 per cent, of which 20 per cent was DCIS.[42] The overdiagnosis in the Netherlands has been calculated with a mathematical model, and is estimated to be 10 per cent.[43] This is partly explained by the lower recall and FP rate in the Netherlands[35] compared with other countries. DCIS accounts for 16 per cent of all screen-detected cancers in the Netherlands.[28] Despite their generally favourably prognosis, women treated for DCIS report increased distress and impaired mental health and concerns about recurrence and death, similar to women with BC.[44,45] So far, analysing the impact of the personality characteristic trait anxiety on distress and QoL has not been performed before in this particular group of women. Therefore, we suggest examining the short- and long-term psychological consequences in women with screen-detected DCIS and analyse the impact of HTA on these effects. In addition, we recommend to improve the provided information concerning treatment options and prognosis of screen-detected DCIS. In addition, the effect of providing evidence based information in women with screen-detected DCIS on distress, QoL and health care utilization should be examined.

Finally, we are interested in women who are diagnosed with BC during the interval of the screening program. In the Netherlands, annually 13000 women are diagnosed with BC, of which 4500 are screen-detected BC, and 1800 are considered as interval BC.[35] Of the interval BC at least 25 per cent is reviewed as a false-negative screening mammogram in the previous round.[32] We believe it is important to investigate the amount of distress and impairment in QoL in this particular group of women with interval BC. Because these women were reassured after a normal screening mammogram, but are nevertheless diagnosed with BC. We expect that these women are being more concerned and thus, are seeking more reassurance despite the regular follow-up protocol, and as a consequence have an increased health care utilization. When examining the exact needs and concerns of this group of women it will possible to offer a tailor-made follow-up protocol, which will be able to prevent ongoing distress and increased health care utilization.

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Chapter 9

Nederlandse samenvatting

Nederlandse samenvatting

Bevolkingsonderzoek naar borstkanker en de psychologische effecten
In 1960 werd het bevolkingsonderzoek naar borstkanker (BOB) geïmplementeerd met als doel vroege detectie van borstkanker (BK) en reductie van de BK mortaliteit te bewerkstelligen. Recente studies hebben echter gesuggereerd dat screening zeer weinig invloed heeft op de BK mortaliteit.[1-3] Dit terwijl het BOB belangrijke nadelen kent, zoals overdiagnose, overbehandeling en een fout-positief screenings mammogram.[3,4] Daaropvolgend hebben recente studies de screening ter discussie gesteld, waarbij men zich afvraagt of de voordelen van het BOB nog wel opwegen tegen de nadelen.[1-10]
Om te kunnen bijdragen aan deze discussie omtrent het BOB, was het doel van het eerste deel van dit proefschrift te bepalen wat de impact is van een afwijkend screenings mammogram op angst, depressieve symptomen en kwaliteit van leven (KvL). Eveneens werd de impact van de karaktertrek angst op deze psychologische parameters geanalyseerd. De karaktertrek angst betreft de neiging om met een verhoogde angstbeleving te reageren op bedreigende situaties, zoals een mogelijke diagnose BK.[11]

In **hoofdstuk twee** zijn twee groepen met een afwijkend screenings mammogram vergeleken, de groep met de uiteindelijke diagnose BK (N=152) en de groep met een fout-positief screenings mammogram (N=233). In zijn algemeenheid scoren vrouwen met BK hoger op angstbeleving en slechter op KvL dan vrouwen met een fout-positief screenings mammogram. Vrouwen met de karaktertrek angst hebben een hoge angstbeleving en verslechtering van KvL, ongeacht de diagnose fout-positief screenings mammogram of BK. Doorverwezen worden met een afwijkend screenings mammogram leidt tot meer histologische biopten en frequente poliklinische bezoeken in de groep met een fout-positief screenings mammogram.

In **hoofdstuk drie** is onderzocht of de timing van een afwijkend screenings mammogram van invloed is op de psychologische parameters. We hebben vrouwen vergeleken die zijn doorverwezen na een eerste screenings mammogram (N=186) met vrouwen die al eerder een screenings mammogram hebben ondergaan (N=296). Bij *alle* vrouwen wordt een hoge score op angstbeleving gevonden voordat de diagnose bekend is. Deze effecten worden versterkt door de karaktertrek angst. Doorverwezen worden na een eerste screenings mammogram veroorzaakt een nog hogere score op angstbeleving, met name bij vrouwen zonder de karaktertrek angst.

In **hoofdstuk vier** zijn vrouwen met de diagnose benigne borstafwijking doorverwezen na een afwijkend screenings mammogram (N=363) vergeleken met vrouwen doorverwezen met een palpabele benigne afwijking in de borst (N=401). Vrouwen doorverwezen na een afwijkend screenings mammogram ervaren meer angst en depressieve symptomen vlak voordat de diagnose gesteld wordt dan vrouwen met een palpabele afwijking in de borst. De vrouwen met een afwijkend screenings mammogram scoren ook slechter op KvL tot een jaar na het stellen van de diagnose. Deze effecten worden met name gevonden bij vrouwen zonder de karaktertrek angst.

Karaktertrek angst bij vrouwen met een (benigne) borstafwijking
Eerdere studies hebben de negatieve impact van de karaktertrek angst op angstbeleving, depressieve symptomen en KvL aangetoond bij vrouwen met BK en een benigne borstafwijking.[12-16] In het tweede deel van dit proefschrift ligt de focus op de impact van de karaktertrek angst op de zorgconsumptie en op de mate van angstbeleving, depressieve symptomen en KvL bij vrouwen met benigne of maligne (borst) ziekte. Hiermee hebben we onderzocht of de eerdere bevindingen ten aanzien van de karaktertrek angst veroorzaakt worden door *alleen* het karakter of ook door de combinatie van de karaktertrek angst *en* de eventuele diagnose BK. Hiervoor hebben we vrouwen met de verdenking van BK vergeleken met vrouwen die gepland werden voor een operatie vanwege galstenen. De groep vrouwen met galsteenziekte werd gekozen omdat in deze groep reeds eerder was aangetoond dat de karaktertrek angst een negatieve invloed heeft op KvL en persisterende klachten na de operatie.[17,18]

In **hoofdstuk vijf** hebben we de zorgconsumptie vergeleken tussen vrouwen met BK (N=151) en een benigne borstafwijking (N=440) gedurende het jaar na de diagnose. Vrouwen met een benigne borstafwijking met de karaktertrek angst hebben een hogere zorgconsumptie dan vrouwen met een benigne borstafwijking zonder de karaktertrek angst. Bij vrouwen met BK en de karaktertrek angst werd meer gebruik van psychosociale zorg gevonden. Belangrijkste voorspeller voor zorgconsumptie bij vrouwen met een benigne borstafwijking zijn de karaktertrek angst en lagere scores voor KvL. Bij vrouwen met BK is de (adjuvante) behandeling de belangrijkste voorspeller voor zorgconsumptie.

In **hoofdstuk zes** zijn vrouwen vergeleken met BK (N=152), een benigne borstafwijking (N=205) en galsteenziekte (N=128) om de impact van de karaktertrek angst en de diagnose op angst en depressieve symptomen te bepalen. Vrouwen met de verdenking van BK ervaren meer angstbeleving en

depressieve symptomen dan vrouwen met galsteenziekte. Deze effecten worden versterkt door de karaktertrek angst. Het is de combinatie van BK *en* de karaktertrek angst welke de hoogste mate van stress veroorzaakt.

In **hoofdstuk zeven** zijn vrouwen vergeleken met BK, een benigne borstafwijking en galsteenziekte om de impact van de karaktertrek angst en de diagnose op KvL te bepalen. Bij vrouwen met galsteenziekte nemen de scores van meerdere domeinen van KvL toe na de operatie, vooral bij vrouwen zonder de karaktertrek angst. Bij vrouwen met een benigne borstafwijking zonder de karaktertrek angst neemt de fysieke KvL toe en verbetert de vermoeidheid. Bij vrouwen met BK zonder de karaktertrek angst verslechtert de fysieke KvL en de vermoeidheid. Vrouwen met de karaktertrek angst scoorden slechter op KvL en vermoeidheid op beide meetmomenten dan vrouwen zonder de karaktertrek angst. Met name de combinatie van de karaktertrek angst en BK heeft een negatieve impact op KvL en vermoeidheid.

Discussie

Tegenwoordig is screenen voor borstkanker een vanzelfsprekendheid geworden in de Westerse wereld. Het BOB heeft als belangrijkste doel vroege detectie, om daarmee de mortaliteit van BK te reduceren. In Nederland hebben meerdere studies aangetoond dat het BOB bijdraagt aan de afname van de mortaliteit van BK.[19-21] In andere landen met een langer bestaand BOB werden deze gunstige effecten bevestigd.[22] Echter, als het BOB vroege detectie bewerkstelligt, dat wil zeggen een kleinere tumor ontdekt met minder of geen metastasen, dan verwacht men dat er een afname is van het aantal vergevorderde stadia van BK. Dit is niet het geval gedurende 12 jaar screening in Nederland.[23] Daarnaast is recent nog gesuggereerd dat screening een minimaal effect heeft op de BK mortaliteit.[1-3] Dit conflicterende bewijs wordt deels verklaard doordat de eerdere gevonden afname in BK sterfte is aangetoond in onderzoeken van matige kwaliteit, terwijl de trials met adequate randomisatie geen effect van screening op de mortaliteit van BK hebben bewezen.[3] Meerdere studies hebben gesuggereerd dat de afname in de sterfte van BK bewerkstelligd wordt door de aanzienlijke verbetering van de adjuvante behandeling van BK.[22-26]
Het eerste deel van dit proefschrift laat zien dat de impact van een afwijkend screenings mammogram op angstbeleving, depressieve symptomen en KvL aanzienlijk is en een serieus probleem veroorzaakt. Niet alleen vrouwen met de karaktertrek angst ervaren het diagnostisch proces voor borstafwijkingen als een grote emotionele belasting. Ook vrouwen zonder de karaktertrek angst ervaren

negatieve psychologische effecten tijdens en na het diagnostische proces na een afwijkend screenings mammogram. Bij 79 procent van de vrouwen met de karaktertrek angst werden abnormale waarden op angstbeleving gevonden voordat de diagnose gesteld werd, maar ook bij 30 procent van de vrouwen zonder de karaktertrek angst. Het feit dat vrouwen zonder de karaktertrek angst ook angstig worden impliceert dat doorverwezen worden na een afwijkend screenings mammogram een serieus psychologisch probleem veroorzaakt. Deze vrouwen hebben niet de neiging om snel angstig te worden, waardoor de abnormale waarden op angstbeleving direct worden veroorzaakt door de verdenking op BK. Ons inziens zijn deze bevindingen een ernstig probleem, met name omdat we niet alleen korte termijn effecten hebben gevonden, maar ook lange termijn consequenties. Ondanks dat de hogere scores voor angstbeleving en depressieve symptomen een maand na de diagnose waren afgenomen, was er wel sprake van een verslechtering van KvL tot een jaar na de diagnose, ongeacht de score voor de karaktertrek angst. Dit betekent dat het psychologische probleem na een afwijkend screenings mammogram niet van tijdelijke aard is. De verslechtering van KvL zal een gevolg zijn van de ernstige stress welke vrouwen hebben ervaren ten tijde van het diagnostisch proces. De lange termijn effecten worden bevestigd door het hoge aantal vrouwen (55 procent) dat de polikliniek nog heeft bezocht gedurende het eerste jaar na een fout-positief screenings mammogram. Blijkbaar zijn deze vrouwen niet voldoende gerustgesteld als blijkt dat ze toch geen BK hebben na een afwijkend screenings mammogram. Deze behoefte aan meer geruststelling is niet onverwacht, aangezien de vrouwen worden doorverwezen zonder klachten te hebben van de borst en dat is zeer verontrustend. Deze vrouwen hebben immers geen palpabele afwijking in de borst bemerkt of andere klachten en hadden een afwijkend screenings mammogram totaal niet verwacht, laat staan alle extra (invasieve) onderzoeken welke worden verricht in verband met het afwijkend screenings mammogram. Ook deze bevindingen bevestigen de ernstige impact van een afwijkend screenings mammogram op het psychisch welbevinden. De resultaten zijn in overeenstemming met eerdere reviews ten aanzien van de nadelige psychologische gevolgen van een afwijkend screenings mammogram.[27-30] In tegenstelling tot de meeste studies beschreven in deze reviews, is in onze studie de eerste vragenlijsten set ingevuld *voordat* de diagnose bekend was. Dit betekent een echte baseline meting, waardoor onze bevindingen van nog meer waarde zijn.

Het tweede deel van dit proefschrift toont aan dat vrouwen met de karaktertrek angst slechter scoren op angstbeleving, depressieve symptomen en KvL als zij geconfronteerd worden met de mogelijke diagnose BK in vergelijking met vrouwen

met galsteenziekte. De karaktertrek angst had een significante impact op zorgconsumptie een jaar later bij vrouwen met een benigne borstafwijking. De impact van de karaktertrek angst op KvL was minder belangrijk bij vrouwen met BK of een benigne borstafwijking dan bij galsteenziekte. Hieruit volgt dat de nadelige gevolgen na een afwijkend screenings mammogram gevonden bij vrouwen met de karaktertrek angst worden veroorzaakt door de combinatie van verdenking op BK *en* de karaktertrek angst, en niet alleen door de karaktertrek angst zelf.

Dit proefschrift laat zien dat een afwijkend screenings mammogram ernstige psychologische gevolgen heeft, ongeacht de karaktertrek angst. In Nederland is de kans op een fout-positief screenings mammogram 9 procent als een vrouw 13 keer meedoet aan de screening.[31] In vergelijking met andere landen is deze kans relatief laag. Dit wordt verklaard door het lagere doorverwijs percentage en de lagere kans op een fout-positief screenings mammogram in Nederland.[31] De kans op een fout-positief screenings mammogram wordt geschat op 49 procent na 10 mammogrammen in de Verenigde Staten en op 21 procent in Noorwegen.[32,33] De verwachting is dat de psychologische nadelen gevonden in dit proefschrift nog ernstiger zullen zijn in bijvoorbeeld de Verenigde Staten gezien de hogere kans op een fout-positief screenings mammogram.
Aangezien het BOB aangeboden wordt aan gezonde vrouwen, is het belangrijk dat de nadelen van de screening tot een minimum beperkt blijven. Uiteraard heeft elk screenings programma bepaalde nadelen, maar de voordelen moeten wel ruimschoots opwegen tegen de nadelen. Dit proefschrift toont aan dat nadelige psychologische gevolgen bij *alle* vrouwen na een afwijkend screenings mammogram werden gevonden. Aangezien het gezonde vrouwen betreft zonder klachten of symptomen van de borst, beschouwen wij deze gevolgen als ernstige en onnodige effecten van het BOB. Met name omdat er recent is aangetoond dat de screening een minimale impact heeft op de BK mortaliteit[1-3], zijn wij van mening dat de balans tussen de voor- en nadelen van het BOB niet meer ten faveure van screening is te noemen. Op basis van eerdere bevindingen en dit proefschrift delen wij de mening van andere auteurs om de rationale van het BOB opnieuw te evalueren.[5,10,25]

Op basis van de bevindingen van dit proefschrift willen wij bewerkstelligen dat zolang het BOB continueert, de informatievoorziening omtrent het BOB verbeterd moet worden. Op dit moment is de informatie betreffende het BOB enkel ten faveure van screening zonder de ernstige nadelen te noemen.[3,6-8,34,35] Mede hierdoor overschatten vrouwen hun risico op BK en de voordelen van screening en zijn dus niet correct geïnformeerd.[36,37] Wij pleiten voor een goede informatievoorziening betreffende voor- *en* nadelen van het BOB. Daarbij moet vooral ook het risico op overdiagnose en de aanzienlijke psychologische consequenties na een fout-positief screenings mammogram genoemd worden. Met behulp van deze betere informatievoorziening kunnen vrouwen beter beslissen of zij willen deel nemen aan het BOB.

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Chapter 10

List of publications

Curriculum Vitae

Dankwoord

List of publications

CMG Keyzer-Dekker, L van Esch, J De Vries, MF Ernst, GAP Nieuwenhuijzen, JA Roukema, AFW van der Steeg. An abnormal screening mammogram causes more anxiety than a palpable lump in benign breast disease.
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Curriculum Vitae

Claudia Keyzer-Dekker werd op 28 juli 1973 geboren in Amsterdam. Haar schooltijd bracht zij door op Het Hoefblad en het St. Ignatiuscollege in Purmerend. Na het afronden van haar Atheneum in 1991, behaalde zij in 1992 haar propedeuse Medische Biologie (UvA) en in 1995 haar propedeuse Medische Informatiekunde (UvA). Uiteindelijk werd zij in 1995 ingeloot voor de studie Geneeskunde (UvA). In 1996 behaalde zij haar propedeuse en in 1999 haar doctoraal diploma (beide cum laude). In 1999 begon zij met haar co-schappen en heeft zij onderwijs gegeven bij de afdeling Anatomie & Embryologie in het AMC (bij dr. F.M.M. Griffioen, prof. dr. R.J. Oostra). In oktober 2002 behaalde zij cum laude haar arts-examen (UvA). Hierna was zij werkzaam als arts-assistent Heelkunde in het AvL (bij dr. F. van Coevorden). In juni 2003 ging zij werken als arts-assistent Heelkunde in het OLVG (bij dr. N.J.M. Out).
In januari 2005 begon zij met haar opleiding tot Chirurg in het MCA (opleider prof. dr. A.B. Bijnen, vervolgens dr. W.H. Schreurs). In juli 2007 vervolgde zij gedurende twee jaar haar opleiding in het VUmc (opleider prof. dr. J.A. Rauwerda). In december 2010 voltooide zij haar opleiding tot Chirurg in het MCA, met als differentiatie Oncologische en Gastro-Intestinale Chirurgie. Gedurende haar opleiding werd in 2008 het wetenschappelijk onderzoek voor dit proefschrift opgestart in samenwerking met de UvT.
In 2011 is zij vier maanden werkzaam geweest als Chirurg in het RKZ. Vanaf mei 2011 heeft zij vervolgens vijf maanden gewerkt als Fellow Kinderchirurgie in het VUmc (bij prof. dr. H.A. Heij en drs. Chr. Sleeboom). Per 1 december 2011 is zij gestart met haar opleiding tot Kinderchirurg in het UMCG (opleider drs. R. van Baren), in combinatie met wetenschappelijk onderzoek naar galgangatresie (dr. J.B.F. Hulscher).

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Lieve Barbera, ik ben er trots op al zo ontzettend lang jouw vriendin te zijn, je bent een echte steun geweest in al die jaren vanaf de middelbare school tot nu toe. Vele avonden samen op stap, bijkletsen met een kop thee en samen sporten, het is altijd gezellig! Jouw relativeringsvermogen is onuitputtelijk gebleken in al die (turbulente) jaren!

Lieve Bouke, ik ben zo blij dat je al zo lang mijn vriendinnetje bent. Vele avonden samen uit geweest onder andere in Flaine, echt een fantastische tijd. Samen tennissen is echt een groot genot, vooral daarna thee leuten of colaatjes light drinken en heel veel bijpraten is tijdens alle hectiek van de afgelopen jaren zeer aangenaam geweest. Heel bijzonder om samen in Rome én Groningen op stap te zijn geweest, wat is ons volgende uitje?

Lieve Iris, vanaf het eerste jaar geneeskunde kennen we elkaar en hebben we heel wat uren samen doorgebracht in de collegezalen, op Plein J, op de Nieuwmarkt of bij Asklepios. Samen met jou een avondje bijpraten vliegt voorbij en dan hebben we nog niet alles besproken! Dank voor al die gezelligheid!

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